Report on the Deliberation Results

September 4, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Tracleer Pediatric Dispersible Tablets 32 mg
[Non-proprietary name]	Bosentan Hydrate (JAN*)
[Applicant]	Actelion Pharmaceuticals Japan Ltd.
[Date of application]	March 31, 2015

[Results of deliberation]
In the meeting held on August 28, 2015, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the product is 6 years and 1 day. The drug product is classified as a powerful drug. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
- The applicant is required to develop and appropriately implement a risk management plan.
- Because of the very limited number of patients in the Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data are collected on a specific number of patients, thereby identifying the characteristics of the treated patients. Data on the safety and efficacy of the product should be collected without delay, and necessary measures should be taken to ensure the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 17, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Tracleer Pediatric Dispersible Tablets 32 mg
[Non-proprietary name]	Bosentan Hydrate
[Applicant]	Actelion Pharmaceuticals Japan Ltd.
[Date of application]	March 31, 2015
[Dosage form/Strength]	Each dispersible tablet contains 32 mg of bosentan (as monohydrate).
[Application classification]	Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage, and (8) Drug in an additional dosage form
[Items warranting special mention]	
	Orphan drug (Drug Designation No. 161 of 2003 [15 *yaku*], Notification No. 0131015 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated January 31, 2003)
[Reviewing office]	Office of New Drug II

Review Results

August 17, 2015

[Brand name]	Tracleer Pediatric Dispersible Tablets 32 mg
[Non-proprietary name]	Bosentan Hydrate
[Applicant]	Actelion Pharmaceuticals Japan Ltd.
[Date of application]	March 31, 2015

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in treatment of pulmonary arterial hypertension in children has been demonstrated and that its safety is acceptable in view of its observed benefits. The occurrence of hepatic function disorders, thrombocytopenia, anemia, and decreased hemoglobin should be investigated in the post-marketing surveillance and other activities.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]
Pulmonary arterial hypertension

[Dosage and administration]
The usual dosage of bosentan for infants and children is 2 mg/kg twice daily (morning and evening) administered orally after being dispersed in a small amount of water. The maximum dose is 120 mg/dose (240 mg/day).

[Conditions for approval]
- The applicant is required to develop and appropriately implement a risk management plan.
- Because of the very limited number of patients in the Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data are collected on a specific number of patients, thereby identifying the characteristics of the treated patients. Data on the safety and efficacy of the product should be collected without delay, and necessary measures should be taken to ensure the proper use of the product.

Review Report (1)

July 8, 2015

I. Product Submitted for Registration

[Brand name]	Tracleer Pediatric Dispersible Tablets 32 mg
[Non-proprietary name]	Bosentan Hydrate
[Applicant]	Actelion Pharmaceuticals Japan Ltd.
[Date of application]	March 31, 2015
[Dosage form/Strength]	Each dispersible tablet contains 32 mg of bosentan (as monohydrate).
[Indication]	Pulmonary arterial hypertension
[Dosage and administration]	The usual dosage of bosentan for infants and children is 2 mg/kg twice daily (morning and evening) administered orally after being dispersed in a small amount of water. The maximum dose is 120 mg/dose (240 mg/day).

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Bosentan Hydrate (hereinafter referred to as "bosentan") is an endothelin receptor antagonist synthesized by Roche (Switzerland). In Japan, the clinical development program of bosentan was undertaken by Actelion Pharmaceuticals Japan Ltd. Tracleer Tablets 62.5 mg containing bosentan as the active ingredient was approved in April 2005 for the indication of "pulmonary arterial hypertension (only in patients in WHO functional class III or IV)." An additional indication of "pulmonary arterial hypertension (in patients in WHO functional class II)" was approved in November 2012. Tracleer Tablets 62.5 mg is widely used for the treatment of pulmonary arterial hypertension (PAH) in adults. Outside Japan, bosentan was approved in the United States (US) in 2001 and the European Union (EU) in 2002 for the treatment of World Health Organization (WHO) functional class (FC) III and IV PAH, and the indication was subsequently expanded to include WHO-FC II PAH in the US and EU in 2008 and 2009, respectively. As of July 2015, bosentan has been approved in 68 countries including the US and European countries.

PAH is a progressive fatal disease. PAH is pathologically similar in adults and children but progresses more rapidly with a poorer prognosis in children than in adults (Sandoval J *et al*. *J Am Coll Cardiol*. 1995;25:466-474; van Loon RL *et al*. *Circulation*. 2011;124:1755-1764). In current clinical practice, drugs approved for adult PAH are used in pediatric patients with PAH at doses adjusted on the basis of efficacy and safety data obtained in adult patients, and no drug has yet been approved in Japan for the treatment of pediatric PAH.

Tracleer Pediatric Dispersible Tablets 32 mg (hereinafter referred also to as the "pediatric formulation of bosentan") containing bosentan as the active ingredient is administered orally after being dispersed in water. The pediatric formulation is palatable for children and can be divided into 4 equal parts to allow weight-based dose-adjustment. Outside Japan, the clinical development of bosentan for the treatment of pediatric PAH began with the start of a clinical study in May 2001, and its approval was granted in the EU in July 2009. The pediatric formulation of bosentan has been approved in the EU, Switzerland, and Mexico as of July 2015.

In Japan, the Japanese Society of Pediatric Cardiology and Cardiac Surgery submitted a request for the clinical development of the pediatric formulation of bosentan. The Study Group on Unapproved and Off-label Drugs of High Medical Need organized by the Ministry of Health, Labour and Welfare (MHLW) assessed the pediatric formulation of bosentan as a drug with "High Medical Needs," and the MHLW requested that the pediatric formulation be developed (Notification No. 0406-1 of the Research and Development Division, Health Policy Bureau, MHLW and Notification No. 0406-1 of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau [PFSB], MHLW, dated April 6, 2012). In response to the MHLW's request, the applicant started a clinical study in [redacted] 20[redacted] and filed a new drug application, claiming that the efficacy and safety of bosentan in the treatment of pediatric PAH have been demonstrated in Japanese and foreign clinical studies. Bosentan was designated as an orphan drug for the intended indication of "pulmonary arterial hypertension" in January 2003 (Drug Designation No. 161 of 2003 [15 *yaku*]).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Bosentan Hydrate, the active ingredient of the drug product (pediatric dispersible tablets), is identical to the drug substance used in the manufacture of Tracleer Tablets 62.5 mg for which the applicant has obtained an approval.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

The drug product is a dispersible tablet which has a cross-score line and contains 33.045 mg of the drug substance (equivalent to 32 mg of bosentan). The drug product contains the following excipients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, light anhydrous silicic acid, tartaric acid, Flavor, aspartame, acesulfame potassium, and magnesium stearate.

2.A.(2).2) Manufacturing process

The drug product is manufactured through a process that consists of the following steps: blending, sieving, milling, and tableting. Process control parameters and values have been established for the tableting step.

2.A.(2).3) Control of drug product

[redacted]

2.A.(2).4) Stability of drug product

The main stability studies of the drug product are shown in Table 1. Photostability testing demonstrated that the drug product is photostable.

Table 1. Stability studies of the drug product

Study	Primary batch	Storage condition	Storage container	Storage period
Long-term testing	3 pilot batches 3 production batches	25°C, 60%RH	Double-sided aluminum foil blister pack	48 or 60 months
Accelerated testing		40°C, 75%RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when packed in a double-sided aluminum foil blister pack and stored at room temperature.

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.B.(1) Novel excipient

The Flavor used in the drug product contains Excipient I, a novel excipient that has not ever been used in pharmaceutical products.

2.B.(1).1) Specifications and stability

PMDA concluded that there is no major problem with the specifications or stability of the Excipient I.

2.B.(1).2) Safety

Based on the submitted data, PMDA concluded that there are no major problems with the safety of the Excipient I when used in the proposed amount and manner.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Model of persistent pulmonary hypertension of the newborn (Attached document, 4.2.1.1.1)

Surgery was performed on pregnant Columbia-Rambouillet ewes under general anesthesia between 120 and 128 days of gestation. The fetal heart and great arteries were exposed through a fetal thoracotomy, and the ductus arteriosus in utero was partially occluded by ligation with a cotton ligature thread for umbilical cord. The in-utero sheep fetus model of persistent pulmonary hypertension of the newborn (PPHN) was generated through the above procedure. During surgery, catheters for hemodynamic monitoring were placed in the main pulmonary artery, aorta, and other major arteries of the fetal lambs, and a catheter for drug delivery was placed in the left pulmonary artery. At 3 to 12 days post-surgery, 10 or 50 mg of bosentan was administered to the fetal lambs in the PPHN model group (n = 5, gestational age of 131 to 140 days) over 30 minutes through the catheter placed in the left pulmonary artery. Fetal lambs without ligation of the ductus arteriosus (n = 4, gestational age of 130 to 142 days) were used as controls. At 3 to 8 days post-surgery, bosentan was administered to the control animals in the same manner as for the PPHN animals. While pulmonary vascular resistance (PVR) decreased in both the PPHN and control groups after administration of bosentan, the PPHN group had a 25% reduction from baseline in PVR, which was higher than that in the control group (16%). No changes were observed in heart rate, pH, blood oxygen partial pressure (PO_2), or blood carbon dioxide partial pressure (PCO_2) in either group after administration of bosentan.

3.(i).B Outline of the review by PMDA

PMDA's view:

Although the submitted primary pharmacodynamic data were obtained from a study using a PPHN model, not a PAH model, the decrease in PVR observed in fetal lambs in the study is considered to be helpful in prediction of the efficacy of bosentan in pediatric PAH patients. The pharmacological effects of bosentan on PAH have already been evaluated for the initial application for Tracleer Tablets 62.5 mg. There seem to be no differences in the pathological condition of increased PVR and the mechanism of action of bosentan (vasodilatory action) between children and adults with PAH. Therefore, bosentan is expected to be therapeutically effective in pediatric PAH patients.

3.(ii) Summary of pharmacokinetic studies

No data have been submitted.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Repeated oral dose toxicity studies of bosentan were conducted in juvenile rats.

3.(iii).A.(1) Repeat-dose toxicity

In the repeated dose toxicity studies in juvenile rats, decreases were observed in reduced body weight gain, decreased weights of the testis and epididymis, and decreased sperm count after administration of bosentan. The no observed adverse effect level (NOAEL) was determined to be 15 mg/kg/day. The area under the plasma concentration-time curve from time 0 to 24 hours after dosing (AUC_{0-24}) at the NOAEL ranged from 11,800 to 168,000 ng·h/mL. The exposure in juvenile rats was compared with that in pediatric patients treated with bosentan 2 mg/kg twice daily. The AUC_{0-24} values in juvenile rats were 1.5- to 21.3-fold the AUC_{0-24} (7879 ng·h/mL) in the group of younger pediatric PAH patients (3 months to 2 years of age) and 1.3- to 19.0-fold the AUC_{0-24} (8820 ng·h/mL) in the group of older pediatric PAH patients (2 to 12 years of age).

3.(iii).A.(1).1) Twenty-five-day repeated oral dose range-finding study in juvenile rats (Attached document 4.2.3.5.4.1, reference data)

Male and female juvenile Wistar rats (n = 6 per sex) received oral doses of vehicle (0.5% methylcellulose or bosentan 60, 300, or 1500 mg/kg/day for 25 days between post-natal days 4 and 28. No treatment-related deaths occurred. Dose-dependent reductions in body weight gain and body weight were observed in the bosentan groups as compared with the control group. While auditory function was not affected, decreased locomotor activity was observed in males in the ≥60 mg/kg/day groups and females in the 1500 mg/kg/day group. This was attributed by the applicant to decreased body weight. Based on the above results, the appropriate maximum dose in toxicity studies in juvenile rats was considered by the applicant to be 135 mg/kg/day, at which body weight gain was estimated to be reduced by approximately 10%.

3.(iii).A.(1).2) Eighteen-, 66-, or >81-day repeated oral dose toxicity study in juvenile rats (Attached document, 4.2.3.5.4.2)

Male and female juvenile Wistar rats (n = 20 per sex) received oral doses of vehicle (0.5% methylcellulose) or bosentan 15, 45, or 135 mg/kg/day for 18 days (post-natal days 4 to 21), 66 days (post-natal days 4 to 69), or >81 days (post-natal days 4 to >84). No treatment-related deaths occurred. In the ≥45 mg/kg/day groups, food consumption and body weight gain markedly decreased in a dose-dependent manner in male and female rats until around post-natal days 18 and 46, respectively, which eventually resolved. Serum inorganic phosphorus levels were high in males in the ≥45 mg/kg/day groups. In the 135 mg/kg/day group, relative heart weights markedly increased without any histopathological findings. Relative weights of the testis and epididymis and sperm count decreased in males in the 135 mg/kg/day group, and the decreases were considered by the applicant to be related to bosentan. However, no effects on the morphology or motility of sperms were observed. Decreased femoral length was observed on post-natal day 21 in females in the ≥45 mg/kg/day groups and males in the 135 mg/kg/day group and persisted until post-natal day 70 in females in the ≥45 mg/kg/day groups. This finding was attributed by the applicant to decreased body weight resulting from reduced body weight gain. No other effects of the treatment were seen in behavior, development, learning, memory, or fertility. Based on the above, the NOAEL was determined by the applicant to be 15 mg/kg/day.

3.(iii).B Outline of the review by PMDA

PMDA asked the applicant to discuss the toxicological significance of decreases in male reproductive organ weights observed in the repeated dose toxicity study in juvenile rats and the effect of decreased sperm count, which was observed in the high-dose group in the same study, on fertility.

The applicant's response:

Although the testis and epididymis weights decreased in the high-dose group, no histopathological abnormalities were observed. Testicular toxicity of endothelin receptor antagonists includes dilatation and atrophy of the seminiferous tubules (Owen K *et al*., *Regul Toxicol Pharmacol*. 2012;64:95-103), but neither tubular dilatation nor tubular atrophy was observed in the toxicity study. Therefore, the decrease in male reproductive organ weights is considered secondary to reduced body weight gain and of no toxicological significance. The change is thus considered to be reversible because the effect on the male reproductive organ is expected to be reduced when the effect on body weight gain is decreased by temporary discontinuation of treatment or by other means. While sperm count decreased in the high-dose group, the rate of pregnancy failure in this group was comparable to the historical data from the laboratory, and the sperm counts in individual male rats in the pairs that failed to achieve pregnancy were similar to those in the control group. In addition, no effects were observed on their mating performance. These results suggest that the pregnancy failure observed was not caused by decreased sperm count but was just coincident. In consideration of the fact that sperm counts decreased without any associated effects on sperm morphology, motility, or fertility, the change was considered to be reversible and attributable to reduced body weight gain. The applicant considers that sperm counts decreased have no toxicological significance.

PMDA's view:

The applicant explained that findings in male reproductive organs were attributable to reduced body weight gain. In light of the facts that no histopathological abnormalities were found in male reproductive organs and that there was no effect on fertility, the applicant's explanation is acceptable. Bosentan is unlikely to cause toxicity relatively specific to children during treatment. However, children may be more susceptible to toxicity similar to that observed in adults because reduced body weight gain can affect bone growth and because the threshold value at which body weight gain was reduced in juvenile rats was 45 mg/kg/day, which was lower than that in mature rats (1000 mg/kg/day). Therefore, data from clinical studies should also be taken into account in evaluation of the safety of bosentan in pediatric PAH patients. PMDA considers that except for the above, no concerns arose from the data obtained from the toxicity studies in juvenile animals.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

4.(i).A Summary of the submitted data

The proposed pediatric dispersible tablet formulation and the approved film-coated (FC) tablet formulation were used in the clinical development program of bosentan for use in pediatric patients with PAH. Plasma concentrations of bosentan and its metabolites were determined by liquid chromatography/tandem mass spectrometry, and the lower limit of quantification was 1.00 ng/mL for bosentan and 2.00 ng/mL for the main metabolite, Ro48-5033 (a metabolite formed by hydroxylation of the dimethylethyl group). In the clinical study in Japanese pediatric PAH patients (Study AC-052-377), dried blood spots were used to determine blood concentrations of bosentan and Ro48-5033 (the lower limit of quantification, 2.00 or 20.0 ng/mL for bosentan and 2.00 ng/mL for Ro48-5033). Values of pharmacokinetic parameters are expressed as mean ± standard deviation unless otherwise specified.

4.(i).A.(1) Bioequivalence between the proposed and approved formulations (Attached document, 5.3.1.2; Study AC-052-116)

In a 2-treatment, 2-period crossover study, 16 healthy non-Japanese male adults received a single oral dose of two bosentan 32 mg dispersible tablets or one bosentan 62.5 mg FC tablet in each of the 2 treatment periods separated by a washout period of 7 to 14 days. The geometric mean ratios (90% confidence intervals [CIs]) of the dispersible tablets to the FC tablet for the maximum plasma concentration (C_{max}) and the area under the concentration-time curve from 0 to time t (AUC_{0-t}) were 0.84 (0.67-1.05) and 0.89 (0.80-0.98), respectively, for bosentan and 0.71 (0.57-0.90) and 0.84 (0.76-0.92), respectively, for Ro48-5033. This study did not show bioequivalence (BE) between the 2 formulations.

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Precautions on interchangeability between the proposed and approved formulations

The strength of bosentan contained in 2 dispersible tablets (64 mg) is nearly the same as that in one FC tablet (62.5 mg), but BE has not been demonstrated between the proposed and approved formulations. In consideration of the above, PMDA asked the applicant to explain what measures it plans to take to prevent the interchangeable use of the 2 formulations.

The applicant's response:

In Study AC-052-116, BE was evaluated between the dispersible and FC tablets, and the geometric mean ratios (90% CIs) of the dispersible tablets to the FC tablet for C_{max} and AUC_{0-t} were 0.84 (0.67-1.05) and 0.89 (0.80-0.98), respectively. C_{max} fell outside the predefined BE range of 0.8 to 1.25. Since bosentan is intended for long-term use in patients with PAH, AUC is considered to be most relevant to its efficacy and safety. Taking into account the above and the fact that the geometric mean ratio of AUC_{0-t} for the dispersible tablets was 89% of that for the FC tablet in Study AC-052-116, the applicant considers that exposure to bosentan does not significantly differ between the 2 formulations. Data from Study AC-052-356 of the FC tablets and Studies AC-052-365 and AC-052-373 of the dispersible tablets

(administered twice daily [b.i.d.]) in non-Japanese pediatric PAH patients and those from Study AC-052-377 of the dispersible tablet in Japanese pediatric PAH patients were plotted to evaluate the relationships between the AUC_{τ} and C_{max} of bosentan and Ro48-5033 and the body weight-based dose of bosentan. The results showed a similar distribution of these parameters between the FC tablet and dispersible tablet formulations, indicating that there is no marked difference in exposure between the 2 formulations.

In pediatric PAH patients who are currently receiving the bosentan FC tablets, their dose is presumably determined based on the dosing regimens of the FC tablets (Table 2) in the foreign clinical study (AC-052-356), which are presented as reference data in the "Clinical Studies" section of the package insert for Tracleer Tablets 62.5 mg. However, the FC tablet has no score line and is not intended to be used on the basis of patient body weight. In contrast, the dispersible tablet as the proposed commercial formulation is scored so that the tablet is easily divided into 4 equal parts and that patients receive doses based on their body weights. When the dispersible tablet becomes available in clinical practice, pediatric PAH patients should be treated with the dispersible tablets, not the approved FC tablets. Table 2 shows the body weight-based dosing regimens of the dispersible tablet. Consequently, the dose would be reduced in patients with a body weight of 10 to 15 kg, 20 to 27 kg, or 40 to 50 kg when treatment is switched from the FC tablet formulation to the dispersible tablet formulation.

In consideration of the above, the applicant proposed that the package insert include a precautionary statement advising that the interchangeable use of the FC tablet and dispersible tablet formulations should be avoided. In addition, the package insert will advise that patients who have been treated with the FC tablets based on the reference data presented in the package insert of Tracleer Tablets 62.5 mg should be carefully monitored by increasing the frequency of hospital visits if the treatment is switched to the dispersible tablet formulation.

Table 2. Reference data on the dosage of FC tablet and dispersible tablet formulations

FC tablet formulation			Dispersible tablet formulation	
Body weight	Initial dose [a]	Maintenance dose	Body weight	Dose (b.i.d.)
			≥4.0 to <7.0 kg	8 mg
			≥7.0 to <11.0 kg	16 mg
≥10 to ≤20 kg	31.25 mg once daily	31.25 mg b.i.d.	≥11.0 to <15.0 kg	24 mg
			≥15.0 to <19.0 kg	32 mg
>20 to ≤40 kg	31.25 mg b.i.d.	62.5 mg b.i.d.	≥19.0 to <23.0 kg	40 mg
			≥23.0 to <27.0 kg	48 mg
			≥27.0 to <31.0 kg	56 mg
			≥31.0 to <35.0 kg	64 mg
			≥35.0 to <39.0 kg	72 mg
>40 kg	62.5 mg b.i.d.	125 mg b.i.d.	≥39.0 to <43.0 kg	80 mg
			≥43.0 to <47.0 kg	88 mg
			≥47.0 to <51.0 kg	96 mg
			≥51.0 to <55.0 kg	104 mg
			≥55.0 to <59.0 kg	112 mg
			≥59.0 kg	120 mg

[a] Administered for the first 4 weeks of treatment

PMDA's view:

The fact should not be overlooked that the dispersible tablet and the FC tablet were not proven to be bioequivalent. The applicant plotted the relationships between the AUC_{τ} and C_{max} of bosentan and Ro48-5033 and the body weight-based dose of bosentan using data from the foreign clinical studies in non-Japanese pediatric PAH patients and Study AC-052-377, and the results showed a similarity in distribution between the formulations. However, because of the limited number of pediatric PAH patients evaluated in the clinical studies, the similarity in distribution is too weak to support the conclusion that exposure to bosentan is similar between the 2 formulations. Also in the light of optimal dosing in pediatric PAH patients, physicians need to be advised to choose the dispersible tablet formulation for use in pediatric PAH patients and to avoid the interchangeable use of the FC and dispersible tablet formulations. In pediatric PAH patients who have been treated with the FC tablet based on the reference data presented in the package insert of Tracleer Tablets 62.5 mg, the dose may be changed when the dosing regimen is switched to that specified for the dispersible tablet formulation. This in turn may result in an altered exposure. There would also be some cases in which the treatment is switched from the FC tablet formulation to the dispersible tablet formulation with a similar strength. Even in such cases, the exposure to bosentan may be altered because BE between the 2 formulations has not been demonstrated. Therefore, patients should be carefully monitored especially early after formulation switching. Based on the above, PMDA considers it reasonable that the applicant plans to provide precautionary advice stating that the interchangeable use of the 2 formulations should be avoided and that patients should be carefully monitored particularly early after formulation switching because of a possible change in exposure.

4.(i).B.(2) Effects of food

Effects of food have been evaluated for the FC tablet, but no food effect studies have been conducted for the proposed commercial formulation (dispersible tablet). BE has not been demonstrated between

the proposed dispersible tablet formulation and the FC tablet formulation. Considering the above, PMDA asked the applicant to explain the effects of food on the pharmacokinetics of the proposed dispersible tablet formulation.

The applicant's response:
A dissolution test was conducted to examine the dissolution profiles of 3 formulations (62.5-mg FC tablet, 32-mg dispersible tablet, and 5% suspension of bosentan) with 2 types of reconstitution diluents (pH 6.8 for both diluents) with different surfactant concentrations. The test confirmed that ≥85% of each of the formulations dissolved within 15 minutes. Since bosentan is classified as a Biopharmaceutics Classification System Class II compound with high permeability and low solubility, the difference in formulation is very unlikely to affect its bioavailability (BA) during the processes from ingestion to absorption; therefore, the BA of the dispersible tablet formulation is considered to be similar to that of the FC tablet formulation. Although BE between the 2 formulations has not been demonstrated, differences in their pharmacokinetics were negligible. These formulations are thus considered to have similar in-vivo dissolution profiles, and the effects of food are unlikely to differ between these formulations. Accordingly, the effects of food on the dispersible tablet formulation were considered to be similar to those on the FC tablet formulation.

PMDA's view:
Since BE has not been demonstrated between the FC tablet formulation and the proposed dispersible tablet formulation, the applicant should have conducted a clinical study to examine the effects of food on the proposed dispersible tablet formulation. However, the applicant explained that the results of a study that compared the dissolution profiles of the formulations and the physicochemical properties of bosentan suggested similar BA between the FC tablet formulation and the proposed dispersible tablet formulation, indicating a negligible difference in pharmacokinetics between the 2 formulations. The applicant further explained that the effects of food on the pharmacokinetics of the proposed dispersible tablet formulation were considered to be similar to those of the FC tablet formulation and that the lack of food effect on pharmacokinetics of the FC tablet formulation indicates that the those of the proposed dispersible tablet formulation would not be affected by food. PMDA considers that the applicant's explanation is acceptable and that the pharmacokinetics of the proposed dispersible tablet formulation is unlikely to be affected by food, as with the approved FC tablet formulation.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) Study in Japanese pediatric patients (Attached document, 5.3.5.2.2; Study AC-052-377)

In an open-label, uncontrolled study, 6 Japanese pediatric PAH patients[1)] aged 1 to 13 years orally received the dispersible tablets of bosentan at 2 mg/kg b.i.d., and the pharmacokinetics of bosentan and

[1)] In a subject, sildenafil citrate was accidentally administered prior to blood sampling for blood drug concentration measurement at 7.5 hours post-dose. Blood concentration data at 7.5 hours and 12 hours post-dose for this subject were excluded from analysis and were not used for the calculation of pharmacokinetic parameters.

its metabolites at Week 12 were evaluated. The estimated plasma concentration[2)] of bosentan reached C_{max} (589.75 ± 292.30 ng/mL) at 2.00 hours after dosing, and the AUC_{τ} was 2888.77 ± 2226.20 ng·h/mL. The estimated plasma concentration of Ro48-5033, the main metabolite, reached C_{max} (75.03 ± 57.04 ng/mL) at 0.50 hours after dosing, and the AUC_{τ} was 420.22 ± 349.49 ng·h/mL.

4.(ii).A.(2) Studies in non-Japanese pediatric patients

4.(ii).A.(2).1) Study AC-052-356 (Attached document, 5.3.3.2.1)

In an open-label, parallel-group comparative study, the pharmacokinetics of bosentan and its metabolites were evaluated in non-Japanese pediatric PAH patients aged 3 to 15 years (18 subjects evaluated for pharmacokinetics). The bosentan FC tablets were used in the study. Patients were to receive bosentan orally according to the following dosing schedule: in the low body weight group (10 to ≤20 kg), at 31.25 mg once daily (q.d.) from Day 1 to Week 4 and at 31.25 mg b.i.d. from Week 5 onward (31.25 mg q.d. at Week 12 visit); in the intermediate body weight group (>20 to ≤40 kg), at 31.25 mg b.i.d. from Day 2 to Week 4 (62.5 mg q.d. on Day 1) and at 62.5 mg b.i.d. from Week 5 onward (62.5 mg q.d. at Week 12 visit); and in the high body weight group (>40 kg), at 62.5 mg b.i.d. from Day 2 to Week 4 (125 mg q.d. on Day 1) and at 125 mg b.i.d. from Week 5 onward (125 mg q.d. at Week 12 visit).

Table 3 shows the pharmacokinetic parameters of bosentan and its main metabolite in plasma after a single dose and multiple doses in the respective groups.

Table 3. Pharmacokinetic parameters in non-Japanese pediatric PAH patients after administration of bosentan

		t_{max}[a] (h)	C_{max}[b] (ng/mL)	$AUC^{b,c}$ (ng·h/mL)	$t_{1/2}$[b] (h)
Bosentan					
Low body weight group	Day 1	1.0	959 (69)	5453 (56)	4.7 (40)
	Week 12	2.5	685 (77)	3496 (49)	6.0 (61)
Intermediate body weight group	Day 1	2.5	815 (108)	6118 (55)	5.3 (35)
	Week 12	1.0	1136 (85)	5428 (79)	5.6 (25)
High body weight group	Day 1	4.0	1709 (39)	10777 (32)	4.2 (44)
	Week 12	1.8	1200 (50)	6124 (27)	5.3 (38)
Ro48-5033					
Low body weight group	Day 1	6.0	52.9 (73)	492 (80)	
	Week 12	1.7	87.6 (46)	511 (41)	
Intermediate body weight group	Day 1	6.0	46.3 (110)	465 (86)	
	Week 12	0.0	95.0 (103)	712 (115)	
High body weight group	Day 1	6.0	106 (89)	946 (60)	
	Week 12	5.0	114 (86)	713 (53)	

n = 6 per group

[a] Median

[b] Geometric mean (coefficient of variation [%])

[c] Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) for Day 1 and AUC_{τ} for Week 12.

[2)] In this study, concentrations of bosentan and its metabolites in whole blood were determined in dried blood spots, and their plasma concentrations were estimated by the formula below:
Estimated plasma C_{max} or AUC_{τ} = whole blood C_{max} or AUC_{τ}/[1 – hematocrit level (%)/100]

4.(ii).A.(2).2) Study AC-052-365 (Attached document, 5.3.3.2.2)

In an open-label, uncontrolled study, the pharmacokinetics of bosentan and its metabolites were evaluated in non-Japanese pediatric PAH patients aged 2 to 11 years (35 subjects evaluated for pharmacokinetics). The bosentan dispersible tablets were used in the study. Subjects orally received bosentan at 2 mg/kg b.i.d. for 4 weeks and then at 4 mg/kg b.i.d. for 8 weeks. The pharmacokinetic parameters measured at Week ≥2 are shown in Table 4.

Table 4: Pharmacokinetic parameters in non-Japanese pediatric PAH patients after administration of bosentan

Measured substance	Dose	Number of subjects	t_{max}[a] (h)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)
Bosentan	2 mg/kg	11[b]	3.0	733 ± 482	4364 ± 2909
	4 mg/kg	35	3.0	1193 ± 1166	5716 ± 5467
Ro48-5033	2 mg/kg	11[b]	0.5	84 ± 45	593 ± 382
	4 mg/kg	35	3.0	142 ± 192	739 ± 681

[a] Median
[b] Number of subjects from whom blood samples were collected both after administration at 2 mg/kg and after a dose increase to 4 mg/kg to determine pharmacokinetics

4.(ii).A.(2).3) Study AC-052-373 (Attached document, 5.3.3.2.3)

In an open-label, parallel-group, comparative study, the pharmacokinetics of bosentan and its metabolites were evaluated in non-Japanese pediatric PAH patients aged 0 to 11 years (58 subjects evaluated for pharmacokinetics). The bosentan dispersible tablets were used in the study. Subjects orally received bosentan at 2 mg/kg b.i.d. or 3 times daily (t.i.d.) for 24 weeks. The pharmacokinetic parameters at Week 4 are shown in Table 5.

Table 5. Pharmacokinetic parameters in non-Japanese pediatric PAH patients after administration of bosentan

Measured substance	Dosing frequency	Number of subjects	t_{max}[a] (h)	C_{max}[b] (ng/mL)	$AUC_{0\text{-}24}$[b] (ng·h/mL)
Bosentan	b.i.d.	31	3.0	959.6 ± 824.1	9995.2 ± 6384.0
	t.i.d.	27	3.0	729.1 ± 733.7	9359.6 ± 7541.4
Ro48-5033	b.i.d.	31	3.0	123.4 ± 79.4	1635.8 ± 1050.9
	t.i.d.	27	3.0	98.0 ± 111.8	1251.4 ± 1002.3

[a] Median
[b] Values corrected on a 2 mg/kg dose basis

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Differences in pharmacokinetics between Japanese and non-Japanese pediatric PAH patients

PMDA asked the applicant to explain differences in pharmacokinetics of bosentan between Japanese and non-Japanese pediatric PAH patients.

The applicant's response:

Table 6 shows the pharmacokinetic parameters of bosentan observed in pediatric PAH patients who received bosentan at 2 mg/kg b.i.d. in the Japanese and foreign clinical studies. The exposure in the Japanese pediatric PAH patients tended to be slightly lower than that in the non-Japanese pediatric PAH patients.

Table 6. Pharmacokinetic parameters in Japanese and non-Japanese pediatric PAH patients after administration of bosentan at 2 mg/kg b.i.d.

		Number of subjects	C_{max} (ng/mL)	AUC (ng·h/mL)
Study AC-052-377	Japanese	5	589.75 ± 292.30	2888.77 ± 2226.20 [a]
Study AC-052-365	Non-Japanese	11	733 ± 482	4364 ± 2909 [a]
Study AC-052-373		31	959.6 ± 824.1	9995.2 ± 6384.0 [b]

[a] AUC_{τ}
[b] $AUC_{0\text{-}24}$

The baseline characteristics of subjects enrolled in the Japanese and foreign clinical studies were examined to find causal factors for the above difference. There were differences in age, body weight, severity of PAH, and concomitant PAH drugs between the Japanese and non-Japanese patient populations, but all these differences were minor. Individual factors were also examined for their effects on exposure, but no clear effects were detected. It has been demonstrated that the pharmacokinetics of bosentan is similar in healthy Japanese and non-Japanese adults and that there is no marked difference in pharmacokinetic characteristics between Japanese and non-Japanese adult PAH patients (the data submitted in the application for Tracleer Tablets 62.5 mg). While it remains unclear why exposure to bosentan in the Japanese pediatric PAH patients was lower than that in the non-Japanese pediatric PAH patients, an analysis of distribution of exposures (AUC_{τ}) in individual subjects showed that exposure in the Japanese pediatric PAH patients fell within the distribution range of exposure in the non-Japanese pediatric PAH patients. Therefore, the above results may have been attributable to high variability in exposure in the limited number of Japanese pediatric PAH subjects. Based on the above, the applicant considers that no substantial difference in the pharmacokinetics of bosentan exists between Japanese and non-Japanese patients.

PMDA's view:

Due to the limited pharmacokinetic data from Japanese pediatric PAH patients evaluated in clinical studies, it is difficult to draw a clear conclusion about the similarity in pharmacokinetics between Japanese and non-Japanese pediatric PAH patients. However, an analysis of distribution of exposure to bosentan (AUC_{τ}) in individual subjects in the Japanese and foreign clinical studies involving pediatric PAH patients showed that distribution in the Japanese pediatric PAH patients fell within the range of distribution in the non-Japanese pediatric PAH patients. In light of the above, together with similarities in pharmacokinetics between Japanese and non-Japanese adult PAH patients, PMDA considers it

acceptable to assume that no marked difference in pharmacokinetics exists between Japanese and non-Japanese pediatric PAH patients.

4.(ii).B.(2) Effects of age on the pharmacokinetics of bosentan

PMDA asked the applicant to discuss differences in the pharmacokinetics of bosentan between pediatric and adult PAH patients and the effects of age on pharmacokinetics.

The applicant's response:

In view of the development process in children, factors in the absorption process (e.g., gastric emptying time, membrane permeability, gastric pH, intestinal transit time, intestinal surface area, protein binding, and changes in expression of metabolic enzymes and transporters) may affect the pharmacokinetic profiles of bosentan. The geometric mean C_{max} and AUC_{τ} in adult PAH patients receiving the FC tablets of bosentan at 125 mg b.i.d. (the recommended clinical dose) was 1878 ng/mL and 8149 ng·h/mL, respectively (data from non-Japanese PAH patients in Study AC-052-357 included in the previous application data package). The C_{max} and AUC_{τ} in children (Table 3) were lower than those in adults probably because of a difference in maturation of the absorptive capacity between children and adults. However, there were no definite age-specific differences in exposure (AUC_{τ}) in pediatric PAH patients receiving bosentan at 2 mg/kg b.i.d. in the Japanese and foreign clinical studies. Based on the above, the applicant considers that although the exposure to bosentan in the pediatric PAH patients receiving the pediatric dispersible tablets at a body weight-based dose did not clearly differ from that in adult PAH patients, age is unlikely to substantially affect the pharmacokinetics of bosentan in pediatric patients.

PMDA's view:

Results of the analysis of the pharmacokinetic data from the Japanese and foreign clinical studies in pediatric PAH patients receiving bosentan at 2 mg/kg b.i.d showed a high variability but no distinct tendency of age-group-specific differences in exposure. Therefore, age is unlikely to affect the pharmacokinetics of bosentan in pediatric patients.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted evaluation data, namely the results from a Japanese phase III study, a Japanese long-term study, a foreign phase I study, and 4 foreign phase III studies. The applicant also submitted the results from a foreign phase III study as reference data [for BE and pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. The major results of the studies are shown below.

4.(iii).A.(1) Phase I study (Attached document, 5.3.1.2; Study AC-052-116 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label study was conducted to evaluate the pharmacokinetics, safety, and tolerability of the bosentan FC and dispersible tablet formulations in 16 healthy Caucasian male adults at 1 center

outside Japan. This study employed a 2-treatment, 2-period crossover design (with a washout period of 7 to 14 days). Subjects received a single oral dose of one FC 62.5 mg tablet or 2 dispersible 32 mg tablets of bosentan in each of the 2 treatment periods. All the 16 receiving the study drug completed the study and were included in the safety analysis set.

Adverse events were reported in none of the subjects receiving an FC tablet but were reported in 2 subjects receiving the dispersible tablets (headache in 1; headache and diarrhoea in 1). A causal relationship between the adverse events and the study drug was ruled out. No deaths, serious adverse events, or adverse events leading to study drug discontinuation were reported.

There were no clinically significant changes in laboratory test results, vital signs, or electrocardiograms, nor were any marked differences shown in clinical findings between the 2 formulations.

4.(iii).A.(2) Japanese phase III study (Attached document, 5.3.5.2.2; Study AC-052-377 [[redacted] 20[redacted] to [redacted] 20[redacted]]) and its extension study (Attached documents, 5.3.5.2.3 and 5.3.5.2.4; Study AC-052-378 [ongoing since [redacted] 20[redacted]; data cutoff, [redacted] [redacted], 20[redacted])

An open-label, uncontrolled study (AC-052-377) was conducted to evaluate the efficacy, safety, tolerability, and pharmacokinetics of the dispersible tablet of bosentan in Japanese pediatric PAH patients (target sample size, 5 subjects) at 9 centers in Japan. An open-label, uncontrolled study (AC-052-378) was conducted at 8 centers in Japan to evaluate the long-term efficacy, safety, and tolerability of bosentan in patients who had completed Study AC-052-377 and met the eligibility criteria (target sample size, 6 subjects).

In Study AC-052-377, subjects orally received bosentan at 2 mg/kg b.i.d. for a 12-week duration, which was defined as the efficacy evaluation period. Subjects who completed treatment in the efficacy evaluation period entered into Study AC-052-378, an extension study of Study AC-052-377 in which the subjects were to receive bosentan at the same dosing regimen used in the efficacy evaluation period until approval or termination of development of the bosentan dispersible tablet formulation. Subjects weighing ≥59 kg were to receive bosentan at 120 mg b.i.d.

The key inclusion criteria are shown below:

- Age 0 to <15 years
- Body weight ≥4 kg
- WHO-FC II, III, or IV
- Patients with a diagnosis of PAH confirmed by right heart catheterization[3)] performed during the screening period

[3)] Data from right heart catheterization performed before screening (between 31 to 90 days before the start of study treatment) were allowed to be used. However, if any change in the severity of PAH was noted by the investigator or subinvestigator during screening after right heart catheterization, data from right heart catheterization performed before screening were not allowed to be used as baseline data.

    - Resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg
    - PVR ≥240 dyn·sec·cm^{-5}
    - Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure ≤15 mmHg
- PAH diagnosed as:
    - Idiopathic or heritable PAH or
    - PAH associated with congenital heart disease

In Study AC-052-377, concomitant diuretics or calcium channel blockers were to be administered at a fixed dose during the 7 days before and on the day of the right heart catheterization at screening and at Week 12. During the efficacy evaluation period excluding the 7 days before, and the day of, the right heart catheterization, the dose of diuretics or calcium channel blockers was allowed to be reduced, discontinued, or resumed within a range not exceeding the dose given at the time of right heart catheterization at screening. Oral prostaglandin I_2 (PGI_2) preparation (beraprost sodium) or phosphodiesterase 5 (PDE-5) inhibitors (sildenafil citrate, tadalafil), if used concomitantly, were to be administered at a fixed dose during the period beginning at least 90 days before right heart catheterization at screening and ending at the end of the efficacy evaluation period. Use of any endothelin receptor antagonist (ERA) or intravenous epoprostenol sodium was prohibited at 30 days before right heart catheterization at screening. In the event of discontinuation of these drugs before the start of study treatment, they had to be discontinued at least 30 days before right heart catheterization at screening.

In Study AC-052-378, concomitant use of any ERA or parenteral PGI_2 preparation was prohibited, and a change in the dose of concomitant oral PGI_2 preparations (beraprost sodium) or PDE-5 inhibitors (sildenafil citrate, tadalafil) was not allowed in principle.

The results in the efficacy evaluation period and the extension period are presented below.

4.(iii).A.(2).1) Efficacy evaluation period

All 6 subjects treated with the study drug were included in the safety analysis set and the per-protocol set (PPS). The PPS was used for the primary efficacy analysis.

The change in PVR index (PVRI) from baseline to Week 12 was evaluated as the primary efficacy endpoint, and the results are shown in Table 7.

Table 7. Change in PVRI (dyn·sec·cm^{-5}·m^2) from baseline to Week 12 (PPS)

Number of subjects	6
Baseline	
Mean ± SD	907.7 ± 494.9
Median (min, max)	775.5 (306, 1729)
Change at Week 12	
Mean ± SD	-4.0 ± 258.6
(95% CI)	(-275.4, 267.4)
Median (min, max)	37.5 (-406, 378)

SD, standard deviation; min, minimum; max, maximum; and CI, confidence interval.

The change in WHO-FC from baseline to Week 12 was a secondary endpoint, and the results are shown in Table 8.

Table 8. Change in WHO-FC from baseline to Week 12 (PPS)

Number of subjects	4
Baseline	
WHO-FC I	0 (0)
WHO-FC II	100 (4)
WHO-FC III	0 (0)
WHO-FC IV	0 (0)
Change at Week 12	
Improved	0 (0)
Unchanged	100 (4)
Worsened	0 (0)

% (number of subjects)
Subjects aged ≥4 years at baseline were evaluated for WHO-FC.

Among safety findings, the incidence of adverse events was 83.3% (5 of 6 subjects). The adverse events reported were nasopharyngitis (2 subjects), abdominal pain (1), adenoviral upper respiratory infection (1), anaemia, aspartate aminotransferase (AST) increased (1), asthma (1), dermatitis diaper (1), dry skin (1), epistaxis (1), myalgia (1), pyrexia (1), blood phosphorus increased (1), and phrenic nerve paralysis (1).

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 16.7% (1 of 6 subjects, blood phosphorus increased).

No deaths occurred. A serious adverse event was reported in 1 subject (adenoviral upper respiratory infection), but its causal relationship to the study drug was ruled out.

No adverse events leading to study drug discontinuation were reported.

4.(iii).A.(2).2) Extension period

All 6 subjects enrolled during the efficacy evaluation period entered into the extension period and were included in the safety analysis set and the full analysis set (FAS). The FAS was used for the primary efficacy analysis. During the extension period, 2 subjects discontinued study treatment due to withdrawal of consent (1) and meeting the exclusion criteria (1).

The duration (mean ± standard deviation) of treatment with bosentan including the efficacy evaluation period (excluding a dose interruption period) was 322.3 ± 78.7 days.

Changes in WHO-FC from baseline during the efficacy evaluation period were assessed. At Week 24, 0 of 4 subjects (0%) improved, 4 of 4 subjects (100%) remained unchanged, and 0 of 4 subjects (0%) worsened. At Week 48, 0 of 2 subjects (0%) improved, 2 of 2 subjects (100%) remained unchanged, and 0 of 2 subjects (0%) worsened.

Safety was analyzed. The incidence of adverse events occurring during the period between the baseline in the efficacy evaluation period and Week 52 was 83.3% (5 of 6 subjects). The adverse events were nasopharyngitis (4 subjects), pyrexia (2), dry skin (2), vomiting (2), dermatitis diaper (1), epistaxis (1), influenza (1), abdominal pain (1), adenoviral upper respiratory infection (1), anaemia (1), AST increased (1), asthma (1), C-reactive protein increased (1), conjunctivitis allergic (1), cough (1), erythema (1), myalgia (1), otitis media (1), pharyngitis (1), pneumonia (1), retinal vein occlusion (1), blood phosphorus increased (1), and phrenic nerve paralysis (1).

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 16.7% (1 of 6 subjects, blood phosphorus increased).

No deaths were reported. Serious adverse events occurred in 2 subjects (adenoviral upper respiratory infection and pneumonia in 1 and retinal vein occlusion in 1), but all of the events were assessed as unrelated to study treatment.

No adverse events leading to study drug discontinuation were reported.

4.(iii).A.(3) Foreign phase III studies

4.(iii).A.(3).1) Study AC-052-356 (Attached document, 5.3.3.2.1 [20 to 20])

An open-label, uncontrolled study was conducted to evaluate the pharmacokinetics, tolerability, safety, and efficacy of a single dose and multiple doses of the bosentan FC tablets in non-Japanese pediatric PAH patients at 2 centers outside Japan. The target sample size was 7 subjects (4 on epoprostenol sodium and 3 not on epoprostenol sodium) in the low body weight group (10 to ≤20 kg), 6 subjects (3 on epoprostenol sodium and 3 not on epoprostenol sodium) in the intermediate body weight group (>20 to ≤40 kg), and 6 subjects (3 on epoprostenol sodium and 3 not on epoprostenol sodium) in the high body weight group (>40 kg).

The period of 12 weeks after the start of bosentan administration was defined as the evaluation period, in which subjects orally received bosentan based on body weight according to the dosing regimens presented in Table 9. In the extension period, subjects received multiple doses of bosentan at the same

dose as that administered from Week 5 onward in the evaluation period. In the event of any problem with tolerability after dose escalation, dose reduction to the initial dose was allowed.

Table 9. Dosing regimens in Study AC-052-356

Treatment group	Evaluation period				Extension period
	Day 1	Day 2 to Week 4	Weeks 5 to 11	Week 12	
Low body weight	31.25 mg q.d.	31.25 mg q.d.	31.25 mg b.i.d.	31.25 mg q.d.	31.25 mg b.i.d.
Intermediate body weight	62.5 mg q.d.	31.25 mg b.i.d.	62.5 mg b.i.d.	62.5 mg q.d.	62.5 mg b.i.d.
High body weight	125 mg q.d.	62.5 mg b.i.d.	125 mg b.i.d.	125 mg q.d.	125 mg b.i.d.

Low body weight group, body weight 10 to ≤20 kg; intermediate body weight group, body weight >20 to ≤40kg; and high body weight group, body weight >40 kg.

The key inclusion criteria were as follows: patients aged 2 to 17 years, weighing ≥10 kg, with PAH (primary PAH or PAH associated with scleroderma or congenital heart disease) of WHO-FC II or III. Patients receiving epoprostenol sodium to treat PAH were eligible for participation in the study if they were clinically stable on epoprostenol sodium for ≥3 months before screening.

All 19 subjects treated with the study drug were defined as "all enrolled patients" and were included in the safety and efficacy analysis populations. Two subjects discontinued study treatment due to adverse events. Of the 2 subjects, 1 subject in the low body weight group was excluded from the efficacy analysis because of lack of data for 12 weeks after baseline. The patient was evaluated only for WHO-FC.

The changes in PVRI and 6-minute walk distance (6MWD) from baseline to Week 12 are shown in Table 10 and Table 11, respectively.

Table 10. Change in PVRI ($dyn \cdot sec \cdot cm^{-5} \cdot m^2$) from baseline to Week 12 (all enrolled patients)

	Low body weight (n = 5)	Intermediate body weight (n = 6)	High body weight (n = 6)
Baseline			
Mean ± SD	1148 ± 848	1151 ± 535	1319 ± 685
Median	877	1102	1274
(min, max)	(285, 2313)	(416, 1909)	(412, 2191)
Change at Week 12			
Mean ± SD	-576 ± 644	-322 ± 146	-47 ± 645
(95% CI)	(-1375, 224)	(-475, -169)	(-724, 629)
Median	-328	-280	-159
(min, max)	(-1374, -13)	(-533, -130)	(-706, 1172)

PVRI was not calculated for 1 subject with a right-to-left shunt due to patent ductus arteriosus (in the low body weight group).

Table 11. Change in 6MWD (m) from baseline to Week 12 (all enrolled patients)

	Low body weight (n = 1)	Intermediate body weight (n = 5)	High body weight (n = 6)
Baseline			
Mean ± SD	424.0	516.0 ± 80.0	482.5 ± 58.8
Median	424.0	523.0	470.5
(min, max)	(424.0, 424.0)	(397.0, 604.0)	(416.0, 573.0)
Change at Week 12			
Mean ± SD	5.0	-24.8 ± 46.7	21.2 ± 67.4
(95% CI)	-	(-82.8, 33.2)	(-49.5, 91.9)
Median	5.0	-57.0	3.5
(min, max)	(5.0, 5.0)	(-61.0, 34.0)	(-67.0, 116.0)

Subjects aged ≥8 years at baseline were evaluated for 6MWD.

Table 12 shows the change in WHO-FC from baseline to Week 12.

Table 12. Change in WHO-FC from baseline to Week 12 (all enrolled patients)

	Low body weight (n = 7)	Intermediate body weight (n = 6)	High body weight (n = 6)
Baseline			
WHO-FC I	0 (0)	0 (0)	0 (0)
WHO-FC II	100.0 (7)	83.3 (5)	50.0 (3)
WHO-FC III	0 (0)	16.7 (1)	50.0 (3)
WHO-FC IV	0 (0)	0 (0)	0 (0)
Change at Week 12			
Improved	14.3 (1)	16.7 (1)	50.0 (3)
Unchanged	71.4 (5)	83.3 (5)	50.0 (3)
Worsened	14.3 (1)	0 (0)	0 (0)

% (number of subjects)

Among safety findings, the incidence of adverse events was 85.7% (6 of 7 subjects) in the low body weight group, 100.0% (6 of 6 subjects) in the intermediate body weight group, and 83.3% (5 of 6 subjects) in the high body weight group. Table 13 shows the adverse events reported in ≥2 subjects.

Table 13. Adverse events reported in ≥2 subjects (all enrolled patients)

	Low body weight (n = 7)	Intermediate body weight (n = 6)	High body weight (n = 6)
Flushing	28.6 (2)	33.3 (2)	0 (0)
Headache	0 (0)	50.0 (3)	0 (0)
Hepatic function abnormal	14.3 (1)	33.3 (2)	0 (0)
Dizziness	0 (0)	33.3 (2)	0 (0)
Pulmonary hypertension	0 (0)	33.3 (2)	0 (0)
Fluid retention	14.3 (1)	0 (0)	16.7 (1)
Pyrexia	14.3 (1)	16.7 (1)	0 (0)
Device-related infection	14.3 (1)	16.7 (1)	0 (0)
Pharyngitis streptococcal	14.3 (1)	16.7 (1)	0 (0)
Pneumonia	14.3 (1)	16.7 (1)	0 (0)
Sore throat NOS	0 (0)	16.7 (1)	16.7 (1)
Upper respiratory tract infection	14.3 (1)	16.7 (1)	0 (0)

% (number of subjects)

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 28.6% (2 of 7 subjects) in the low body weight group, 66.7% (4 of 6 subjects) in the intermediate body weight group, and 33.3% (2 of 6 subjects) in the high body weight group. The adverse event that occurred in ≥2 subjects and for which a causal relationship to the study drug could not be ruled out was hepatic function abnormal in 3 subjects (1 in the low body weight group and 2 in the intermediate body weight group).

No deaths were reported. Serious adverse events occurred in 2 subjects (hepatic function abnormal in 1 in the low body weight group; and tachycardia, hypertension, tremor, dizziness, and central venous catheterisation in 1 in the intermediate body weight group), and their outcomes were reported as resolved.

The adverse event leading to study drug discontinuation was hepatic function abnormal reported in 2 subjects (1 each in the low and intermediate body weight groups).

4.(iii).A.(3).2) Study AC-052-365 (Attached document, 5.3.3.2.2 [[redacted] 20[redacted] to [redacted] 20[redacted]]) and its extension study (Attached document, 5.3.5.2.1; Study AC-052-367 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study (AC-052-365) was conducted at 11 centers outside Japan to evaluate the pharmacokinetics, tolerability, and safety of the bosentan dispersible tablet in non-Japanese pediatric PAH patients. The target sample size was 10 subjects each in the following age groups: 2 to <4 years, 4 to <6 years, and 6 to <12 years. An open-label, uncontrolled study (AC-052-367) was conducted at 11 centers outside Japan to evaluate the long-term tolerability and safety of bosentan in patients who had completed Study AC-052-365 and met the eligibility criteria.

In Study AC-052-365, the period of 12 weeks after the start of bosentan administration was defined as the treatment period. Bosentan was orally administered at 2 mg/kg b.i.d. as the initial dose for the first 4 weeks of the treatment period and at 4 mg/kg b.i.d. as the maintenance dose from Weeks 4 to 12. If bosentan 4 mg/kg b.i.d. was not well tolerated, dose reduction to 2 mg/kg b.i.d was allowed. Subjects weighing ≥30 kg were to receive the maximum initial dose of 64 mg b.i.d. and then the maintenance dose of 120 mg b.i.d. After completing the treatment period, subjects entered into Study AC-052-367, an extension study, and received bosentan at 4 mg/kg b.i.d. until the age of 12 years or until approval or termination of development of the bosentan dispersible tablet formulation. If bosentan 4 mg/kg b.i.d. was not well tolerated, dose reduction to 2 mg/kg b.i.d. was allowed. In the extension period, subjects weighing ≥30 kg were to receive a maximum dose of 120 mg b.i.d., unless dose reduction was necessary, in which case they were receive a maximum dose of 64 mg b.i.d.

The key inclusion criteria were as follows: patients aged 2 to <12 years, weighing ≥4 kg, with idiopathic or familial PAH of WHO-FC II or III. Other inclusion criteria included patient's condition and PAH therapy stable for at least 3 months before screening, and the study enrolled PAH treatment-naïve patients or patients already treated with monotherapy with bosentan or a PGI_2 preparation (intravenous epoprostenol sodium or intravenous or inhaled iloprost) or combination therapy with bosentan and a

PGI_2 preparation (intravenous epoprostenol sodium or intravenous or inhaled iloprost). Patients receiving calcium channel blockers continuously for at least 3 months before screening were eligible for participation in the study.

In Study AC-052-365, concomitant calcium channel blockers or PGI_2 preparations (intravenous epoprostenol sodium, or intravenous or inhaled iloprost) were to be administered at a fixed dose throughout the study period. Concomitant use of sildenafil citrate or ERAs was prohibited.

In Study AC-052-367, concomitant use of calcium channel blockers and PGI_2 preparations (intravenous epoprostenol sodium or intravenous or inhaled iloprost) was allowed. Concomitant use of sildenafil citrate[4)] or ERAs was prohibited.

(a) Treatment period

All 36 subjects treated with the study drug were included in the safety and efficacy analysis populations. Two subjects discontinued study treatment due to administrative and other reasons (1) and death (1).

The change in WHO-FC from baseline to Week 12 was an exploratory efficacy endpoint, and the results are shown in Table 14.

Table 14. Change in WHO-FC from baseline to Week 12 (all-treated set)

Number of subjects	35
Baseline	
WHO-FC I	0 (0)
WHO-FC II	65.7 (23)
WHO-FC III	34.3 (12)
WHO-FC IV	0 (0)
Change at Week 12	
Improved	14.3 (5)
Unchanged	82.9 (29)
Worsened	2.9 (1)

% (number of subjects)
One subject with missing data at Week 12 was excluded from the analysis.

Among safety findings, the incidence of adverse events was 61.1% (22 of 36 subjects), and the adverse events reported in ≥2 subjects were abdominal pain (4 subjects), vomiting (3), abdominal pain upper (2), aggression (2), asthenia (2), bronchitis (2), chest pain (2), fatigue (2), flushing (2), headache (2), nasal congestion (2), pain in extremity (2), pulmonary hypertension (2), tonsillitis (2), and viral infection (2).

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 36.1% (13 of 36 subjects). The adverse events possibly related to the study drug and reported in ≥2 subjects were abdominal pain (4 subjects), chest pain (2), headache (2), nasal congestion (2), abdominal pain upper (2), asthenia (2), flushing (2), and vomiting (2).

4) Excluding additional administration in the case of PAH worsening.

Death occurred in 1 subject (ear infection and right ventricular failure), and a causal relationship to the study drug was ruled out for the adverse events reported as the cause of the death. Serious adverse events occurred in 4 subjects (cough, fatigue, and hypertension in 1 subject; adenoidectomy and bacterial infection in 1; pulmonary hypertension in 1; and ear infection and right ventricular failure in 1). Among these adverse events, pulmonary hypertension was considered to be possibly related to the study drug. However, symptoms began to subside on the first day of treatment with the FC tablets of bosentan at 31.25 mg/kg b.i.d. after completion of the study, and the subject was finally in a stable condition.

Except for the death, no adverse events led to study drug discontinuation.

(b) Extension period

Of 34 subjects who completed Study AC-052-365, 33 subjects entered into the extension period. All of the 36 subjects treated with the study drug in Study AC-052-365 were included in the "all-treated set," which was used for both safety and efficacy analyses. Seventeen subjects discontinued the study during the extension period due to administrative and other reasons (4), withdrawal of consent (5), death (3), disease progression (2), adverse events (1), transplantation (1), and lack of efficacy (1).

The duration (mean ± standard deviation) of treatment with bosentan including the treatment period was 134.7 ± 85.7 weeks.

The change in WHO-FC from baseline during the treatment period was an exploratory efficacy endpoint, and the results are shown in Table 15.

Table 15. Change in WHO-FC from baseline (all-treated set)

	Month 24 (n = 15)	Month 48 (n = 7)	End of study (n = 28)
Baseline			
WHO-FC I	0 (0)	0 (0)	0 (0)
WHO-FC II	80.0 (12)	71.4 (5)	60.7 (17)
WHO-FC III	20.0 (3)	28.6 (2)	39.3 (11)
WHO-FC IV	0 (0)	0 (0)	0 (0)
Change from baseline			
Improved	26.7 (4)	28.6 (2)	39.3 (11)
Unchanged	73.3 (11)	71.4 (5)	53.6 (15)
Worsened	0 (0)	0 (0)	7.1 (2)

% (number of subjects)
Subjects without available data at each time point (including the end of study) were excluded from the analysis.

Among safety findings, the incidence of adverse events was 88.9% (32 of 36 subjects). Adverse events reported in ≥4 subjects were abdominal pain (7 subjects), nasopharyngitis (7), pulmonary arterial hypertension (6), pulmonary hypertension (6), bronchitis (5), upper respiratory tract infection (5), chest pain (4), fatigue (4), flushing (4), headache (4), pneumonia (4), syncope (4), and vomiting (4).

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 41.7% (15 of 36 subjects). The adverse events possibly related to the study drug and reported in ≥2 subjects were abdominal pain (4 subjects), chest pain (3), headache (3), nasal congestion (3), abdominal pain upper (2), asthenia (2), flushing (2), palpitations (2), and vomiting (2).

Deaths occurred in 4 subjects (1 with ear infection and right ventricular failure; 1 with pulmonary arterial hypertension and right ventricular failure; 1 with systemic-pulmonary artery shunt, pneumonia, and respiratory failure; and 1 with cardiac failure), but a causal relationship to the study drug was ruled out for all of the adverse events reported as the cause of the death. The incidence of serious adverse events was 50.0% (18 of 36 subjects), and the serious adverse events reported in ≥2 subjects were device-related infection (3 subjects), pulmonary arterial hypertension (3), pulmonary hypertension (3), fatigue (2), right ventricular failure (2), and systemic-pulmonary artery (2). A causal relationship to the study drug was ruled out for these events, except pulmonary arterial hypertension and pulmonary hypertension reported in 1 subject each.

Adverse events leading to study drug discontinuation occurred in 6 subjects (dyspnoea exertional and autoimmune hepatitis in 1 subject; ear infection and right ventricular failure in 1; pulmonary arterial hypertension, right ventricular failure, and systemic-pulmonary artery shunt in 1; cardiac failure in 1; and pulmonary hypertension in 1). A causal relationship to the study drug was ruled out for these events, except pulmonary hypertension and autoimmune hepatitis reported in 1 subject each.

4.(iii).A.(3).3) Study AC-052-373 (Attached document, 5.3.3.2.3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, randomized, comparative study was conducted at 45 centers outside Japan to evaluate the pharmacokinetics, tolerability, safety, and efficacy of the bosentan dispersible tablets administered at 2 mg/kg b.i.d. and t.i.d. to non-Japanese pediatric PAH patients (target sample size, 64 subjects in total [33 in the b.i.d. group and 31 in the t.i.d. group]). The study consisted of a 24-week evaluation period and a subsequent extension period (for 1 year following completion of the evaluation period).

The key inclusion criteria are shown below:

- Age 3 months to <12 years
- Body weight ≥3.5 kg
- WHO-FC I, II, or III
- mPAP ≥25 mmHg and PCWP ≤15 mmHg
- PAH diagnosed as:
    - Idiopathic or heritable PAH,
    - Persistent PAH after radical surgery for congenital heart disease (PAH persisting for ≥6 months after surgery), or
    - PAH associated with systemic-to-pulmonary shunts including Eisenmenger's syndrome (PVR >8 Wood units and pulmonary-to-systemic blood flow ratio [Qp/Qs] <2)

Patients on calcium channel blockers, bosentan, PGI_2 preparations, or PDE-5 inhibitors at a fixed dose for treatment of PAH for at least 3 months before screening were eligible for participation in the study.

Concomitant calcium channel blockers, PGI_2 preparations, and PDE-5 inhibitors were to be administered at a fixed dose during the study period.

All 64 subjects treated with the study drug (33 in the b.i.d. group and 31 in the t.i.d. group) were included in the safety analysis set and the "all-randomized set." The all-randomized set was used for the primary efficacy analysis. Four subjects (2 in the b.i.d. group and 2 in the t.i.d. group) discontinued study treatment due to adverse events (3 subjects; 2 in the b.i.d. group and 1 in the t.i.d. group) and withdrawal of consent (1 in the t.i.d. group).

The duration of treatment with bosentan (mean ± standard deviation) in this study was 23.6 ± 3.71 weeks in the b.i.d. group and 23.3 ± 5.02 weeks in the t.i.d. group. The proportion of pediatric subjects treated with bosentan for ≥24 weeks was 72.7% (24 of 33 subjects) in the b.i.d. group and 77.4% (24 of 31 subjects) in the t.i.d. group.

The change in PVRI from baseline to the end of study was evaluated as an exploratory efficacy endpoint for the hemodynamic subgroup consisting of subjects who underwent right heart catheterization at least once after the start of study treatment. The results are shown in Table 16.

Table 16. Change in PVRI ($dyn \cdot sec \cdot cm^{-5} \cdot m^2$) from baseline to the end of study (all-randomized set)

	b.i.d. (n = 2)	t.i.d. (n = 2)
Baseline		
Mean ± SD	215.7 ± 70.50	838.6 ± 784.11
Median	215.7	838.6
(min, max)	(166, 266)	(284, 1393)
Change from baseline to the end of study		
Mean ± SD	-55.0 ± 77.71	-160.5 ± 226.98
(95% CI)	(-753.2, 643.3)	(-2199.8, 1878.8)
Median	-55.0	-160.5
(min, max)	(-110, 0)	(-321, 0)

The change in WHO-FC from baseline to the end of study was an exploratory efficacy endpoint, and the results are shown in Table 17.

Table 17. Change in WHO-FC from baseline to the end of study (all-randomized set)

	b.i.d. (n = 33)	t.i.d. (n = 31)
Baseline		
WHO-FC I	27.3 (9)	32.3 (10)
WHO-FC II	36.4 (12)	48.4 (15)
WHO-FC III	36.4 (12)	19.4 (6)
WHO-FC IV	0 (0)	0 (0)
Change from baseline to the end of study	21.2 (7)	9.7 (3)
Improved	75.8 (25)	87.1 (27)
Unchanged	3.0 (1)	3.2 (1)
Worsened		

% (number of subjects)

Safety was analyzed. The incidence of adverse events was 63.6% (21 of 33 subjects) in the b.i.d. group and 67.7% (21 of 31 subjects) in the t.i.d. group. The adverse events reported in ≥2 subjects in either group are shown in Table 18.

Table 18. Adverse events reported in ≥2 subjects in either group (safety analysis set)

	b.i.d. (n = 33)	t.i.d. (n = 31)
Upper respiratory tract infection	18.2 (6)	35.5 (11)
Nasopharyngitis	15.2 (5)	9.7 (3)
Pyrexia	12.1 (4)	22.6 (7)
Pulmonary arterial hypertension	9.1 (3)	3.2 (1)
Diarrhoea	6.1 (2)	12.9 (4)
Bronchitis	6.1 (2)	3.2 (1)
Respiratory tract infection	6.1 (2)	3.2 (1)
Thrombocytopenia	6.1 (2)	0 (0)
Otitis media	6.1 (2)	0 (0)
Vomiting	3.0 (1)	12.9 (4)
Viral infection	3.0 (1)	6.5 (2)
Respiratory tract infection viral	3.0 (1)	6.5 (2)
Rash	3.0 (1)	6.5 (2)
Constipation	3.0 (1)	6.5 (2)
Cough	0 (0)	9.7 (3)
Epistaxis	0 (0)	9.7 (3)
Gastroenteritis	0 (0)	6.5 (2)
Flushing	0 (0)	6.5 (2)

% (number of subjects)

The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 9.1% (3 of 33 subjects) in the b.i.d. group and 16.1% (5 of 31 subjects) in the t.i.d. group. The adverse event possibly related to the study drug and reported in ≥2 subjects in either group was thrombocytopenia (2 in the b.i.d. group and 0 in the t.i.d. group).

Death occurred in 1 subject in the t.i.d. group (bronchopneumonia and pulmonary arterial hypertension), and a causal relationship to the study drug was ruled out for either of the adverse events reported as the cause of the death. Serious adverse events occurred in 4 subjects in the b.i.d. group (cardiac failure, infection, metabolic disorder, and multi-organ failure in 1; cardiac operation in 1; pulmonary arterial hypertension in 1; and loss of consciousness and drug hypersensitivity in 1) and 7 subjects in the t.i.d. group (oxygen saturation decreased, body temperature increased, pyrexia, and gastroenteritis in 1; atrial septal defect repair in 1; bronchopneumonia and pulmonary arterial hypertension in 1; respiratory distress in 1; respiratory tract infection viral in 1; viral infection in 1; and gastroenteritis adenovirus[5)] in 1). All these events were assessed as unrelated to the study treatment.

Adverse events leading to study drug discontinuation were reported in 2 subjects in the b.i.d. group (cardiac failure in 1 and pulmonary arterial hypertension in 1) and 1 subject in the t.i.d. group (pulmonary arterial hypertension and bronchopneumonia). All these events were associated with the worsening of PAH and were assessed as unrelated to the study treatment.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning

PMDA asked the applicant to explain the clinical positioning of bosentan in the treatment of pediatric PAH with discussions on comparison with similar drugs, including choice between, and combination of, bosentan and the similar drugs.

The applicant's response:

According to the treatment algorithm for pediatric idiopathic and heritable PAH (Ivy DD *et al*., *J Am Coll Cardiol*. 2013;62:D117-126), which is the consensus of the Fifth World Symposium on Pulmonary Hypertension held in 2013, patients should be classified into high-risk and low-risk patients according to their risk of morbidity and mortality in order to receive appropriate treatment. Treatment with oral ERAs or PDE-5 inhibitors and inhaled iloprost or treprostinil is recommended for low-risk patients. For high-risk patients, subcutaneous or intravenous treatment with epoprostenol sodium or treprostinil is recommended, and early combination therapy of oral ERAs or PDE-5 inhibitors should be considered. Irrespective of risk levels, patients should be followed-up on a regular basis, and early combination therapy with PAH drugs should be considered. The use of ERAs is recommended for pediatric PAH patients regardless of their risk levels as shown above, and bosentan therapy has been allocated a class of recommendation I with a level of evidence B. In Japan, the Japanese Circulation Society (JCS) published the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases (Guidelines for Diagnosis and Treatment of Cardiovascular Diseases, 2010-2011 JCS Joint Working Group) in 2012, which provide a treatment algorithm for pediatric PAH. In this algorithm, bosentan is recommended for treatment of patients with PAH in WHO-FC III but not mentioned for the treatment

5) An event reported after locking the database

of patients with PAH in WHO-FC II, partly because bosentan was not approved for the treatment of PAH WHO-FC II in Japan at that time (approval of the indication was granted in November 2012).

Guidelines available both in and outside Japan recommend the consideration of combination therapy with PAH drugs for patients in WHO-FC III or IV who do not respond to their current PAH treatment. Of 6 subjects enrolled in the Japanese phase III study (AC-052-377), 5 had received PAH drugs other than bosentan. This suggests a high level of guideline compliance in clinical practice.

In Japan, adult PAH patients are treated according to the treatment algorithm described in the Guidelines for Treatment of Pulmonary Hypertension (JCS2012) (Guidelines for Diagnosis and Treatment of Cardiovascular Diseases, 2010 JCS Joint Working Group). The Japanese treatment algorithm generally follows the one proposed at the Fourth World Symposium on Pulmonary Hypertension (Barst RJ *et al*., *J Am Coll Cardiol*. 2009;54:S78-84), with a minor modification for excluding drugs unapproved in Japan. Except for it, PAH treatment currently provided in and outside Japan is based on the same treatment algorithm. The WHO treatment algorithm was updated at the Fifth World Symposium on Pulmonary Hypertension (Galiè N *et al*., *J Am Coll Cardiol*. 2013;62:D60-72) just to include new PAH drugs and reflect other relatively minor changes, and accordingly the treatment algorithms presented at the Fourth and Fifth World Symposia on Pulmonary Hypertension and the Japanese treatment algorithm are basically the same.

Pediatric PAH is a rare serious disease, and because of a lack of evidence for its treatment, children with PAH are currently treated on the basis of results from large clinical studies in adult PAH patients and the clinical experience of pediatricians (Ivy DD *et al*., *J Am Coll Cardiol*. 2013;62:D117-26). In light of the above, the applicant considers that, except for some modifications in the treatment algorithms for children, important components are shared between the pediatric and adult treatment algorithms, and that basic therapeutic strategies do not differ between children and adults. All these treatment guidelines recommend the use of bosentan as a therapy for PAH patients in WHO-FC II to IV, and the clinical position of bosentan in the treatment of PAH does not differ between adult and pediatric patients.

As discussed above, when the pediatric formulation of bosentan becomes available in clinical practice, it will be the first-line oral agent for pediatric PAH patients because it will be the only drug approved for a pediatric dosing regimen. In addition, the pediatric formulation contains sweetening agents and is designed to be dispersed in a small amount of water before oral use. These features are beneficial for very young patients who cannot take tablets.

PMDA's view:
Pediatric PAH was one of the topics discussed at the Fifth World Symposium on Pulmonary Hypertension in 2013, and the following was pointed out as the difference from the adult PAH: the majority of pediatric cases consists of idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease, whereas cases of PAH associated with connective tissue disease are relatively

rare in children. Treatment of PAH in pediatric patients is based on results of large clinical studies in adult PAH patients and the clinical experience of experts in treatment of pediatric PAH, and the treatment algorithm for pediatric PAH recommends the use of ERAs in both low-risk and high-risk patients with a negative acute vasoreactivity response (Ivy DD *et al*., *J Am Coll Cardiol*. 2013;62:D117-126). The clinical position of bosentan in the treatment of PAH is clearly stated in the latest treatment algorithm, which is mainly intended to be used for adult patients, and bosentan therapy is graded as Class I ("is recommended/is indicated") for patients in WHO-FC II and III and as Class IIa ("should be considered") for patients in WHO-FC IV (Galiè N *et al*., *J Am Coll Cardiol*. 2013;62:D60-72).

In Japan, the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases recommend bosentan for pediatric PAH patients in WHO-FC III and IV. Since the Japanese guidelines have been developed based on the current Western guidelines at that time, the clinical position of bosentan in treatment of pediatric PAH in the Japanese guidelines would be the same as that in the Western guidelines. As a result of the review of the data from clinical studies conducted in and outside Japan for this application [see "4.(iii).B.(3) Efficacy" and "4.(iii).B.(4) Safety"], PMDA considers that the pediatric formulation of bosentan will offer a new therapeutic option for pediatric PAH patients when it becomes available in clinical practice in Japan and that the pediatric dosage form will be beneficial for pediatric patients who cannot take tablets.

4.(iii).B.(2) Use of data from foreign clinical studies

PMDA asked the applicant to discuss similarities and differences in intrinsic and extrinsic ethnic factors between Japanese and non-Japanese patients, to compare the results of clinical studies conducted in and outside Japan, and then to justify the use of data obtained from foreign clinical studies for demonstrating the efficacy and safety of bosentan in Japanese pediatric PAH patients.

The applicant's response is presented in the sections below.

4.(iii).B.(2).1) Intrinsic ethnic factors

A comparison of patient characteristics in the Japanese and foreign clinical studies in pediatric PAH patients (Studies AC-052-356, AC-052-377, AC-052-378, AC-052-365, AC-052-367, and AC-052-373) revealed no major differences in sex, age, height, and body weight among these studies.

In terms of the etiology of PAH, idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease have been reported predominantly in pediatric patients with PAH classified into Group 1 of the clinical classification system for pulmonary hypertension (Nakayama T *et al*., *Journal of Clinical and Experimental Medicine*. 2012;240:95-101). There were no marked differences in etiologies of PAH in pediatric subjects enrolled in the Japanese and foreign clinical studies except for Studies AC-052-365 and AC-052-367which excluded patients with PAH associated with congenital heart disease. The above 3 etiologies of PAH were predominant in pediatric subjects enrolled in the clinical studies, and there was no difference in the distribution of etiologies of PAH in and outside Japan.

In Study AC-052-377 conducted in Japan, 4 subjects aged ≥4 years were evaluable for WHO-FC. All of the 4 subjects were assessed as WHO-FC II. Meanwhile, the majority of subjects in the foreign clinical studies were in WHO-FC II or III. However, WHO-FC II and III are similar in terms of a lack of subjective symptoms at rest and are distinguished from each other only by the degree of physical activities that cause dyspnea, fatigue, or chest pain. Accordingly, there seem to be no major differences in the distribution of patients in terms of WHO-FC between Japan and other countries. Therefore, the applicant considered that data from the foreign clinical studies could be used to demonstrate the efficacy and safety of bosentan, regardless of a difference in WHO-FC status.

The pharmacokinetic analysis showed that the exposure to bosentan was slightly lower in Japanese patients than in non-Japanese patients [see "4.(ii).B.(1) Differences in pharmacokinetics between Japanese and non-Japanese pediatric PAH patients"]. However, results of the analysis of distribution of AUC_τ in individual subjects in Studies AC-052-356, AC-052-365, AC-052-377, and AC-052-373 demonstrated that the plasma concentration of bosentan in Japanese pediatric PAH patients fell within the range of that in non-Japanese PAH patients. The correlation between mean exposure and efficacy was investigated with AUC_τ and pulmonary hemodynamic parameters obtained in one foreign clinical study (AC-052-356) and one Japanese clinical study (AC-052-377). An analysis of relationship between systemic exposure to unchanged bosentan and changes from baseline in pulmonary hemodynamic parameters (mPAP, mean right atrial pressure, cardiac index [CI], and PVRI) at Week 12 showed, within the observed AUC_τ range, no differences in any parameters between the Japanese and non-Japanese clinical studies. In conclusion, at the exposure levels observed in Study AC-052-377, bosentan is expected to produce the same efficacy as seen in the foreign clinical studies.

4.(iii).B.(2).2) Extrinsic ethnic factors

The treatment algorithm for pediatric PAH patients in Japan is nearly the same as that in other countries as stated in "4.(iii).B.(1) Clinical positioning," but there were differences in concomitant PAH drugs used in the applicant's clinical studies due to differences in timing of studies. PDE-5 inhibitors and PGI_2 preparations were mainly used as concomitant drugs in the Japanese clinical study (AC-052-377), whereas epoprostenol sodium, besides PDE-5 inhibitors and PGI_2 preparations, was the concomitant drug frequently used in the foreign clinical studies.

Since pediatric PAH is a rare serious disease, it is ethically unacceptable to prohibit a concomitant use of approved PAH drugs with different mechanisms of action in clinical studies. Therefore, the clinical studies of bosentan enrolled patients who were clinically stable on other PAH drugs at a fixed dose during a certain period prior to the start of study treatment. The enrollment of such patients was expected to make it possible to properly evaluate the efficacy of bosentan while eliminating the potential effects of other drugs to the greatest extent possible, because the efficacy and safety of study drug are evaluated through a comparison of data obtained before and after treatment. In the foreign clinical studies, the concomitant use of epoprostenol sodium, a potent vasodilator, was allowed, and the efficacy of bosentan

was thus evaluated as an additive effect, possibly making it difficult to evaluate the efficacy of bosentan precisely. Besides epoprostenol sodium, PDE-5 inhibitors and oral PGI_2 preparations were used concomitantly with bosentan in these foreign clinical studies. The concomitant PAH drugs were similar with those used in the Japanese studies (AC-052-377 and AC-052-378) and those recommended in the Japanese Guidelines for Treatment of Pulmonary Hypertension (revised version, 2012). The similarity in the concomitant use of these drugs also supports the acceptability of using data from the foreign clinical studies.

PMDA's view:
The results of the analysis of intrinsic ethnic factors suggest that there are no ethnic differences in the pathological condition of PAH in children as in adults and that the distribution of etiologies of PAH is similar in and outside Japan. In addition, the pharmacokinetics of bosentan does not differ significantly between Japanese and non-Japanese patients, and the differences in pharmacokinetics, if any, are unlikely to affect the efficacy and safety of bosentan [see "4.(ii).B.(1) Differences in pharmacokinetics between Japanese and non-Japanese pediatric PAH patients"]. An analysis of extrinsic ethnic factors revealed differences in concomitant use of PGI_2 preparations and PDE-5 inhibitors between Japanese and foreign clinical studies, but the effects of the differences on the efficacy evaluation of bosentan were minimized by enrolling patients whose condition and treatment had been stable for ≥3 months before screening and by prohibiting any change in the type and daily dose of the concomitant drugs. Therefore, extrinsic ethnic factors are considered to have no marked impact on the assessment of the efficacy and safety of bosentan in treatment of PAH. In light of the above, PMDA considered that the efficacy and safety of bosentan in Japanese pediatric PAH patients can be evaluated based on the data obtained from both the Japanese and foreign clinical studies.

4.(iii).B.(3) Efficacy
In Study AC-052-377 in Japanese pediatric PAH patients, the mean change in PVRI from baseline to Week 12, the primary endpoint, showed no improvement, and the median showed a trend toward worsening. Furthermore, no subjects showed improvement in WHO-FC at Week 12.

Despite the above results, the applicant claims that bosentan is expected to be effective in treating Japanese pediatric PAH patients. PMDA asked the applicant to provide a rationale supporting the claim.

The applicant's response:
The results of individual 6 subjects receiving the study drug in Study AC-052-377 are shown in Table 19.

Table 19. Results of individual subjects (Study AC-052-377)

Subject	Etiology	PVRI (dyn·sec·cm^{-5}·m^2)			
		Baseline	Week 12	Change	Percent change
Subject 1	Idiopathic PAH	831	884	53	6.4%
Subject 2	Idiopathic PAH	1200	1578	378	31.5%
Subject 3	Idiopathic PAH	720	582	-138	-19.2%
Subject 4	Idiopathic PAH	1729	1323	-406	-23.5%
Subject 5	PAH associated with congenital heart disease	306	328	22	7.2%
Subject 6	Heritable PAH	660	727	67	10.2%

The change from baseline in PVRI at Week 12 was positive in 4 of the subjects enrolled in Study AC-052-377. No adverse events such as worsening of PAH or similar events were reported by the investigators for any of these 4 subjects. PVRI increased by >20% in 1 subject. In the other 3 subjects, increased PVRI was interpreted by the investigators as not representing worsening of PAH or as probably induced by decreased cardiac output associated with a tendency toward bradycardia noted at Week 12, suggesting that these subjects maintained their baseline condition without experiencing progression of PAH. The 1 subject with >20% increase in PVRI received bosentan for ≥1 year after the start of study treatment and remained stable in WHO-FC II throughout the study period. According to the Fifth World Symposium on Pulmonary Hypertension consensus, the ultimate goal of treatment of pediatric PAH is to improve patient outcome and to allow patients to perform their activities of daily living without limitation (Ivy DD *et al*., *J Am Coll Cardiol*. 2013;62:D117-126). The goal, i.e., allowance of activities of daily living without limitation, seemed to be achieved in this subject. In addition, no adverse events of worsening of PAH or similar events were reported by the investigators or subinvestigators who actually treated the subjects, and the fact suggests that the study treatment arrested the progression of PAH that is progressive disease.

In Studies AC-052-356 and AC-052-373 conducted outside Japan, pulmonary hemodynamic data were obtained to evaluate the efficacy of bosentan in pediatric PAH patients, and high variability in hemodynamics was observed in both studies. In Study AC-052-356, the change from baseline in PVRI at Week 12 (mean ± standard deviation [median]) was -300 ± 537 (-274) dyn·sec·cm^{-5}·m^2, indicating that PVRI decreased after administration of bosentan. In Study AC-052-373, PVRI was measurable in only 2 subjects each in the b.i.d group and the t.i.d. group. The change in PVRI from baseline to Week 24 was -109.9 and 0 dyn·sec·cm^{-5}·m^2 for the 2 subjects in the b.i.d. group and -321.0 and 0[6)] dyn·sec·cm^{-5}·m^2 for the 2 subjects in the t.i.d. group, showing improvement. As presented in Table 20, many subjects showed improvement in WHO-FC from baseline at Week 12, and the proportion of subjects with clinical worsening ranged from 0% to 5.3%. In Study AC-052-367, bosentan was administered for up to 5 years, and the efficacy observed at Week 12 was maintained until the end of the study.

6) Missing PVRI data at completion or discontinuation of the study treatment were imputed with the baseline values.

Table 20. Change from baseline in WHO-FC in foreign clinical studies

Study	Number of subjects	Improved	Unchanged	Worsened
Week 12				
AC-052-356	19	26.3 (5)	68.4 (13)	5.3 (1)
AC-052-365	35	14.3 (5)	82.9 (29)	2.9 (1)
AC-052-373 b.i.d.	33	15.2 (5)	81.8 (27)	3.0 (1)
AC-052-373 t.i.d.	31	9.7 (3)	90.3 (28)	0 (0)
End of the study				
AC-052-367	28	39.3 (11)	53.6 (15)	7.1 (2)
AC-052-373 b.i.d.	33	21.2 (7)	75.8 (25)	3.0 (1)
AC-052-373 t.i.d.	31	9.7 (3)	87.1 (27)	3.2 (1)

% (number of subjects)
Analysis population: all enrolled patients in Study AC-052-356, all-treated sets in Studies AC-052-365 and AC-052-367, and all-randomized set in Study AC-052-373.

In the specified drug use-results survey for approved Tracleer Tablets 62.5 mg, data were collected from patients treated with bosentan between June 10, 2005 and May 19, 2014, and 3279 patients were included in the efficacy analysis. Of the 3279 patients, 779 were children with PAH aged <15 years. The proportions of patients who improved and those who worsened (including deaths) from baseline in WHO-FC were 35.1% (204 of 581 patients) and 5.5% (32 of 581 patients), respectively, at Week 12; 44.9% (236 of 526 patients) and 9.3% (49 of 526 patients), respectively, at Month 12; and 46.6% (212 of 455 patients) and 13.0% (59 of 455 patients), respectively, at Month 24.

Published literature on the efficacy of bosentan in pediatric PAH patients reports cases in which treatment with bosentan and other drugs failed to relieve PAH symptoms or to improve pulmonary hemodynamics, resulting in death or lung transplantation (Ishii T *et al*., *Shinzo*. 2013;45:789-795). In many other case reports, however, bosentan proved to be generally effective in the treatment of PAH (Ivy DD *et al*., *Am J Cardiol*. 2010;106:1332-1338; Hirono K *et al*., *J Thorac Cardiovasc Surg*. 2010;140:346-351; van Loon RL *et al*., *Am Heart J*. 2007;154:776-782; Rosenzweig EB *et al*. *J Am Coll Cardiol*. 2005;46:697-704; Brun H *et al*. *Cardiol Young*. 2007;17:288-294; Simpson CM *et al*., *J Heart Lung Transplant*. 2006;25:469-473; Maiya S *et al*. *Heart*. 2006;92:664-670; and Gilbert N *et al*. *Z Kardiol*. 2005;94:570-574).

As shown above, the efficacy of bosentan in improving pulmonary hemodynamics and WHO-FC status has been demonstrated in the Japanese and foreign clinical studies in adult patients and the foreign clinical studies in pediatric patients. Furthermore, the results of the specified drug use-results survey and the literature published in and outside Japan also suggest the efficacy of bosentan in treating Japanese pediatric PAH patients.

PMDA's view:
In Study AC-052-377 conducted in Japan, the mean change from baseline in PVRI at Week 12, the primary endpoint, showed no improvement, and the median showed a trend toward worsening. Since these results were obtained from the study in a small number of subjects, hemodynamic parameters in

individual subjects were analyzed in detail. The change from baseline in PVRI at Week 12 was negative in 2 of 6 subjects, showing a trend toward improvement, but it was positive in the other 4 subjects with no sign of improvement. Of these 4 subjects, 1 exhibited a distinct increase in PVRI by 31.5% and also showed increased mPAP and decreased CI. While the changes in PVRI in 2 subjects (increased by 6.4% and 10.2%) were not substantial, CI and mixed venous oxygen saturation (SvO_2) decreased in both subjects. The above findings suggest that bosentan was ineffective in these 3 subjects. In the remaining 1 subject, the change in PVRI was 22 dyn·sec·cm^{-5}·m^2, SvO_2 remained unchanged, and CI elevated, suggesting that the subjects was almost stable. In its discussion on the 4 subjects with no improvement in PVRI, the applicant indicated that changes in pulmonary hemodynamics in the subjects were not regarded by the investigator as worsening of PAH and that no adverse events such as worsening of PAH symptoms were reported by the investigators. However, given that Study AC-052-377 was conducted as an open-label uncontrolled study, these are merely subjective opinions of the investigators and should not be given more weight than objective assessment. An evaluation of hemodynamics revealed only 2 subjects showing a definite improvement in hemodynamic parameters including PVRI as the objective primary endpoint. PMDA assessed the efficacy of bosentan, based on the results of hemodynamic evaluation, as effective in 2 subjects, ineffective in 3 subjects, and unchanged in 1 subject.

In Study AC-052-356 conducted outside Japan, the change from baseline in PVRI at Week 12 (mean ± standard deviation [median]) was -300 ± 537 (-274) dyn·sec·cm^{-5}·m^2, indicating an improvement in PVRI following administration of bosentan. In Study AC-052-373, PVRI data were obtained from 2 subjects each in the b.i.d and t.i.d. groups. The change in PVRI from baseline to Week 24 was -109.9 and 0 dyn·sec·cm^{-5}·m^2 for 2 subjects in the b.i.d. group and -321.0 and 0[6)] dyn·sec·cm^{-5}·m^2 for 2 subjects in the t.i.d. group. The results suggest improvement, albeit data obtained from only a small number of subjects.

PAH is a rare disease and is even rarer in children. In children with PAH, the disease is frequently associated with congenital heart disease, and emergency treatment including surgery is required in some cases. In Japan, PAH drugs approved for adult patients have been used in pediatric patients. Under such circumstances, it is understandable that there is a difficulty in conducting a clinical study with a sample size sufficient to demonstrate the efficacy of bosentan in Japanese pediatric PAH patients. Although it is unclear why Study AC-052-377 in Japanese pediatric PAH patients failed to clearly demonstrate the efficacy of bosentan, 2 of the 6 subjects requiring therapeutic intervention in the study responded to the study treatment, and the condition of another subject remained unchanged after treatment. Differences in extrinsic or intrinsic ethnic factors among pediatric PAH patients are considered to be small enough to allow the extrapolation of data from foreign studies to Japanese patients [see "4.(iii).B.(2) Use of data from foreign clinical studies"]. The efficacy and safety of bosentan have been demonstrated in Japanese adult PAH patients (see the Review Report for Tracleer 62.5 mg Tablets [only available in Japanese], an approved drug), and there is unlikely to be any difference in the pathological condition and treatment of PAH between adult and pediatric patients. Taking the above into account, PMDA considers that the

efficacy of bosentan demonstrated in non-Japanese pediatric PAH patients can be expected also in Japanese pediatric PAH patients.

PMDA will make a final decision on the efficacy of bosentan in Japanese pediatric PAH patients, taking account of comments from the Expert Discussion.

4.(iii).B.(4) Safety

4.(iii).B.(4).1) Differences in safety profiles between adult and pediatric patients

PMDA asked the applicant to explain differences in the safety profiles of bosentan between adult and pediatric patients.

The applicant's response:

Table 21 shows the incidences of the major adverse events reported in Japanese and foreign clinical studies in adult and pediatric PAH patients.

Table 21. Incidences of adverse events in Japanese and foreign clinical studies in adult and pediatric PAH patients

	Adult patients			Pediatric patients	
	Foreign study		Japanese study	Foreign study	Japanese study
	Controlled comparative study	Uncontrolled study			
Number of subjects	237 [a]	315 [b]	40 [c]	119 [d]	6 [e]
Upper respiratory tract infection	8.4 (20)	7.9 (25)	2.5 (1)	20.2 (24)	0 (0)
Nasopharyngitis	9.7 (23)	3.5 (11)	57.5 (23)	13.4 (16)	66.7 (4)
Pyrexia	1.3 (3)	2.2 (7)	20.0 (8)	13.4 (16)	33.3 (2)
Vomiting	1.7 (4)	2.5 (8)	10.0 (4)	8.4 (10)	33.3 (2)
Flushing	6.3 (15)	4.4 (14)	7.5 (3)	8.4 (10)	0 (0)
Diarrhoea	5.9 (14)	6.7 (21)	10.0 (4)	8.4 (10)	0 (0)
Pulmonary arterial hypertension	0 (0)	0 (0)	0 (0)	8.4 (10)	0 (0)
Abdominal pain	3.0 (7)	1.6 (5)	10.0 (4)	6.7 (8)	16.7 (1)
Headache	14.3 (34)	9.5 (30)	32.5 (13)	6.7 (8)	0 (0)
Pulmonary hypertension	5.1 (12)	19.0 (60)	2.5 (1)	6.7 (8)	0 (0)
Bronchitis	3.8 (9)	5.1 (16)	12.5 (5)	6.7 (8)	0 (0)
Cough	5.1 (12)	3.2 (10)	12.5 (5)	5.9 (7)	16.7 (1)
Pneumonia	2.5 (6)	2.2 (7)	2.5 (1)	5.0 (6)	16.7 (1)
Epistaxis	3.4 (8)	4.1 (13)	15.0 (6)	5.0 (6)	16.7 (1)
Otitis media	0.4 (1)	0.6 (2)	2.5 (1)	3.4 (4)	16.7 (1)
Influenza	3.8 (9)	1.0 (3)	5.0 (2)	2.5 (3)	16.7 (1)
Pharyngitis	1.3 (3)	0.3 (1)	5.0 (2)	2.5 (3)	16.7 (1)
Anaemia	3.4 (8)	1.9 (6)	10.0 (4)	0.8 (1)	16.7 (1)
AST increased	0.8 (2)	0 (0)	17.5 (7)	0.8 (1)	16.7 (1)
Erythema	0.8 (2)	1.0 (3)	2.5 (1)	0.8 (1)	16.7 (1)
Conjunctivitis allergic	0 (0)	0 (0)	2.5 (1)	0.8 (1)	16.7 (1)
Dry skin	0.4 (1)	0.6 (2)	0 (0)	0 (0)	33.3 (2)
Myalgia	0.8 (2)	0.3 (1)	10.0 (4)	0 (0)	16.7 (1)
Asthma	0 (0)	0.3 (1)	0 (0)	0 (0)	16.7 (1)
C-reactive protein increased	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)
Dermatitis diaper	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)
Adenoviral upper respiratory infection	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)
Phrenic nerve paralysis	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)
Blood phosphorus increased	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)
Retinal vein occlusion	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)

% (number of subjects)
Adverse events with an incidence of ≥5% in any pooled group of pediatric PAH patients
[a] Pooled data set of bosentan groups in Studies AC-052-352 and AC-052-364
[b] Pooled data set of Studies AC-052-354 and AC-052-357
[c] Pooled data set of Studies AC-052-363 and AC-052-372
[d] Pooled data set of Studies AC-052-356, AC-052-367, and AC-052-373
[e] Pooled data set of Studies AC-052-377 and AC-052-378

Only 6 pediatric PAH patients were enrolled in the Japanese clinical studies, AC-052-377 and AC-052-378, and the small number of subjects made it difficult to compare the safety profiles in the Japanese studies with those in other studies. A comparison of data between the foreign pediatric clinical studies and the Japanese and foreign adult clinical studies revealed that adverse events occurring more

frequently in pediatric patients than in adult patients were upper respiratory tract infection (20.2%), nasopharyngitis (13.4%), and pulmonary arterial hypertension (8.4%). Pulmonary arterial hypertension was reported more frequently in pediatric patients (8.4%) than in adult patients (0%); however, this was mainly because the term "pulmonary hypertension" was used to report relevant adverse events during the conduct of the adult clinical studies (excluding Study AC-052-372). In actuality, there was no marked difference between the incidence of pulmonary hypertension in adult patients (2.5%-19.0%, Table 21) and the proportion of pediatric patients experiencing pulmonary arterial hypertension or pulmonary hypertension (0%-14.3%). The incidences of adverse events related to anemia, edema, and abnormal liver function tests, which are characteristic of bosentan, were lower in pediatric patients than in adult patients, but there was no marked difference in the severity or time of onset of the events between adult and pediatric patients.

PMDA's view:

At present, safety data including the occurrence of adverse events in Japanese and foreign clinical studies and the results of an analysis of adverse events characteristic of bosentan (i.e., events related to anemia, edema, and abnormal liver function tests) do not suggest that greater safety concerns may arise from the use of bosentan in pediatric PAH patients than in adult PAH patients. However, bosentan should be prescribed by physicians with adequate knowledge and experience in the treatment of pediatric PAH for the following reasons: (1) bosentan has been evaluated only in a very small number of pediatric patients in clinical studies and (2) the information on long-term safety of bosentan remains insufficient for pediatric PAH patients who are expected to be treated with the drug for a longer period than adult patients. PMDA will make a final decision on the appropriateness of precautionary statements in the package insert, taking account of comments from the Expert Discussion.

4.(iii).B.(4).2) Hepatic function disorders

PMDA asked the applicant to present the proportions of subjects with abnormal liver function tests (alanine aminotransferase [ALT], AST) and the incidences of adverse events related to hepatic function disorder in the Japanese and foreign clinical studies and to discuss the necessity of providing any additional precautionary statement regarding the risk of hepatic function disorders associated with the use of bosentan in children.

The applicant's response:

There were no subjects with increased AST or ALT ≥2-fold the upper limit of normal (ULN) in the Japanese studies. The proportion of subjects with increased AST or ALT ≥2 × ULN in the foreign studies are shown in Table 22.

Table 22. Proportion of subjects with increased AST or ALT ≥2 × ULN in foreign studies

	<1 year (n = 6)	1 to <2 years (n = 15)	2 to <7 years (n = 45)	7 to <15 years (n = 50)
ALT	0 (0)	6.7 (1)	4.4 (2)	8.0 (4)
AST	33.3 (2)	13.3 (2)	8.9 (4)	6.0 (3)

% (number of subjects)
Pooled data set of Studies AC-052-356, AC-052-365, and AC-052-373

In the foreign studies, the proportion of subjects with increased ALT ≥2 × ULN was similar in all age groups, except for the age groups of "<1 year" and "≥15 years," both of which consisted of a small number of subjects. The proportion of subjects with increased AST ≥2 × ULN was 33.3% in those aged <1 year, and this high proportion probably reflects the markedly smaller number of subjects in this age group than in other age groups, suggesting no age-specific trend. Also, no age-specific differences were detected in the time of onset, severity, or seriousness of the relevant adverse events.

The incidences of adverse events related to hepatic function disorder by age in the Japanese clinical studies are shown in Table 23. There was no notable effects of age on the types or incidences of these adverse events. No adverse events related to hepatic function disorder were reported in any of the subjects aged <2 years (21 subjects in the foreign studies and 1 in the Japanese study).

Table 23. Incidences of adverse events related to hepatic function disorder in Japanese and foreign clinical studies

	Foreign clinical study [a]		Japanese clinical study [b]	
	2 to <7 years (n = 45)	7 to <15 years (n = 50)	2 to <7 years (n = 3)	7 to <15 years (n = 2)
Hepatic function abnormal	2.2 (1)	4.0 (2)	0 (0)	0 (0)
AST increased	2.2 (1)	0 (0)	33.3 (1)	0 (0)
ALT increased	2.2 (1)	0 (0)	0 (0)	0 (0)
Autoimmune hepatitis	2.2 (1)	0 (0)	0 (0)	0 (0)
Liver function test abnormal	0 (0)	2.0 (1)	0 (0)	0 (0)
Hepatosplenomegaly	0 (0)	2.0 (1)	0 (0)	0 (0)
Blood bilirubin increased	0 (0)	2.0 (1)	0 (0)	0 (0)

% (number of subjects)
[a] Pooled data set of Studies AC-052-365, AC-052-367, and AC-052-373
[b] Pooled data set of Studies AC-052-377 and AC-052-378

In the Japanese and foreign clinical studies, 10 subjects (9 in the foreign clinical studies and 1 in the Japanese clinical study) experienced adverse events related to abnormal liver function tests or hepatic function disorder. Of the 10 subjects, 5 (all in the foreign clinical studies) required temporary or permanent study drug discontinuation. These adverse events did not tend to occur more frequently in the children than in patients participating in the adult clinical studies. No marked differences in severity or time to onset of these adverse events were found between pediatric and adult patients.

Based on the above, the applicant considers that there is no need to provide any additional precautionary statement regarding the risk of hepatic function disorders or liver function test abnormalities for pediatric use and that the precautions for pediatric use should be the same as those for use in adults.

PMDA's view:

In the Japanese clinical studies, no subjects had an increase in ALT or AST ≥2 × ULN, and only 1 subject experienced an adverse event related to hepatic function disorder. The subject was in the age group of 2 to <7 years and experienced AST increased during the first 2 months of treatment. The event resolved without dose reduction, temporary or permanent study drug discontinuation, or use of additional concomitant drugs. The pooled analysis of foreign clinical studies showed no particular tendency in the incidence or time to onset of adverse events related to hepatic function disorder, age group, or profiles of patients with increased ALT or AST ≥2 × ULN. In the Japanese and foreign clinical studies in pediatric PAH patients, adverse events related to hepatic function disorder or increased ALT or AST were reported in 10 of 125 subjects (8%), of whom 2 subjects required temporary study drug discontinuation and 3 subjects permanent study drug discontinuation. Of the 10 subjects, 7 recovered and 3 did not. Adverse events related to hepatic function disorder occurred less frequently in pediatric PAH patients than in the adult clinical studies. Although it is difficult to rigorously compare data from these different studies, the results of the comparison suggest that there are no marked differences in the incidence of hepatic function disorder between adult and pediatric patients. The post-marketing safety information of bosentan suggest no major concerns related to hepatic function disorder in pediatric PAH patients treated with the drug. Therefore, the risk of hepatic function disorder in pediatric PAH patients is considered to be manageable as in adult PAH patients through monitoring of hepatic function and by other means as described in the package insert of Tracleer Tablets 62.5 mg. Based on the above, PMDA considers that there is no need to provide any additional precautionary statement regarding the risk of hepatic function disorder in pediatric PAH patients.

4.(iii).B.(4).3) Other safety issues

The applicant's explanation on risks associated with bosentan other than hepatic function disorders:

An analysis was performed on the occurrence of anemia-related adverse events, decreased hemoglobin, pancytopenia, decreased white blood cell count, decreased neutrophil count, decreased platelet count, edema-related adverse events, and adverse events related to decreased blood pressure in the Japanese and foreign clinical studies in pediatric PAH patients (a total of 125 subjects from Studies AC-052-356, AC-052-365, AC-052-367, AC-052-373, AC-052-377, and AC-052-378).

Adverse events related to anemia[7)] were reported in 4.8% of subjects (6 of 125 subjects [3 in Study AC-052-367, 2 in Study AC-052-373, and 1 in Study AC-052-377]), and none of them required any dose adjustment (dose reduction or discontinuation) of the study drug.

A decrease in hemoglobin levels to <10 g/dL and by >15% from baseline was reported in 4.8% of subjects (6 of 125 subjects [3 in Study AC-052-365, 2 in Study AC-052-373, and 1 in Study AC-052-377]). Information on action taken for decreased hemoglobin levels (e.g., addition or dose reduction of

7) Events identified by the Standardised MedDRA Query (SMQ) "haematopoietic erythropenia" (MedDRA version 17.0).

concomitant drugs, dose adjustment of the study drug) was not collected in Studies AC-052-365 or AC-052-373. In Study AC-052-377, one subject with decreased hemoglobin required no dose adjustment of the study drug. This subject was receiving an iron preparation, which was introduced before the start of study treatment, for concurrent iron deficiency anemia and received no additional treatment for decreased hemoglobin level.

Pancytopenia, decreased white blood cell count, decreased neutrophil count, or decreased platelet count[8)] were reported in 3.2% of subjects (4 of 125 subjects [1 in Study AC-052-356 and 3 in Study AC-052-373]). The dose of the study drug was adjusted in 2 subjects with thrombocytopenia in Study AC-052-373. Of the 2 subjects, 1 discontinued the study drug temporarily due to platelet count decreased. In the subject, the event resolved, and a causal relationship to the study drug was ruled out. The other subject discontinued the study drug due to worsening of PAH, and platelet count decreased was reported on the day of discontinuation. The event was assessed as related to the study drug.

Adverse events related to edema[9)] were reported in 4.0% of subjects (5 of 125 subjects [3 in Study AC-052-356, 1 in Study AC-052-367, and 1 in Study AC-052-373]), and none of them required dose adjustment of the study drug.

An adverse event related to decreased blood pressure[10)] was reported only in 1 of 125 subjects (0.8%) in Study AC-052-356, and the subject required no dose adjustment of the study drug.

The incidences of anemia-related adverse events, decreased hemoglobin, pancytopenia, decreased white blood cell count, decreased neutrophil count, decreased platelet count, edema-related adverse events, and adverse events related to decreased blood pressure reported in pediatric PAH patients receiving bosentan ranged from 0.8% to 4.8%. Among these adverse events, only thrombocytopenia in 1 subject (0.8%) led to the temporary or permanent discontinuation of the study drug and was assessed as unrelated to the study drug. The above results indicate that adequate precautionary statements on these events are provided in the package insert of approved Tracleer Tablets 62.5 mg. The applicant thus considers it appropriate that similar precautions should be advised for pediatric use.

PMDA's view:
Adverse events reported in association with treatment with bosentan, such as anemia, decreased hemoglobin, decreased platelet count, edema, and decreased blood pressure, are also known to occur with other ERAs, and these adverse events are considered to be due to the vasodilatory effect of ERAs. The results of the Japanese and foreign clinical studies and data from a post-marketing surveillance showed no marked differences in the safety profiles of bosentan, including types of adverse events,

8) Events classified under the MedDRA Preferred Terms (PTs) "pancytopenia," "white blood cell count decreased," "leukopenia," "neutrophil count decreased," "platelet count decreased," and "thrombocytopenia" (MedDRA version 17.0).
9) Events identified by the SMQ "haemodynamic oedema, effusions and fluid overload" (MedDRA version 17.0).
10) An event classified under the MedDRA PT "hypotension" (MedDRA version 17.0).

between adult and pediatric PAH patients. Given the fact that appropriate precautionary statements are provided in the package insert of approved Tracleer Tablets 62.5 mg, PMDA considers that similar precautions for pediatric use are sufficient to ensure the adequate management of these adverse events in clinical practice.

4.(iii).B.(5) Indication

4.(iii).B.(5).1) WHO functional classes

PMDA asked the applicant to explain the efficacy and safety of bosentan by WHO-FC in the Japanese and foreign clinical studies in pediatric PAH patients and to justify why the applicant proposed that the pediatric formulation of bosentan should be indicated for "pulmonary arterial hypertension" regardless of WHO-FC status.

The applicant's explanation:

The changes in PVRI by WHO-FC in the Japanese and foreign clinical studies in pediatric PAH patients are shown in Table 24.

Table 24. Change from baseline in PVRI by WHO-FC in Japanese and foreign clinical studies in pediatric PAH patients ($dyn \cdot sec \cdot cm^{-5} \cdot m^2$)

WHO-FC	I	II	III	IV
AC-052-356 [a]				
Number of subjects	0	13	4	0
Mean ± SD	–	-386.3 ± 422.2	-17.5 ± 827.3	–
(95% CI)	–	(-641.4, -131.2)	(-1333.9, 1298.9)	–
AC-052-373 [b]				
Number of subjects	2	2	0	0
Mean ± SD	-215.5[c]	0[d]	–	–
(95% CI)	–	–	–	–
AC-052-377 [a]				
Number of subjects	0	4	0	0
Mean ± SD	–	23 ± 323	–	–
(95% CI)	–	(-490.9, 536.9)	–	–

Analysis populations: all enrolled patients in Study AC-052-356, all-randomized set in Study 052-373, and PPS in Study AC-052-377..

[a] Change from baseline to Week 12

[b] Change from baseline to Week 24

[c] -109.9 $dyn \cdot sec \cdot cm^{-5} \cdot m^2$ in 1 subject and -321.0 $dyn \cdot sec \cdot cm^{-5} \cdot m^2$ in the other subject.

[d] 0 $dyn \cdot sec \cdot cm^{-5} \cdot m^2$ in both subjects. (In 1 subject, the missing PVRI data at the completion or discontinuation of the study treatment were imputed with the baseline value.)

None of the 25 subjects evaluated for PVRI were assigned to WHO-FC IV. Study AC-052-373 enrolled 2 subjects in WHO-FC I and 2 in WHO-FC II. The change in PVRI in both subjects in WHO-FC II was 0 $dyn \cdot sec \cdot cm^{-5} \cdot m^2$ (the missing PVRI data at the completion or discontinuation of the study treatment in 1 subject were imputed with the baseline value). In Study AC-052-377, no PVRI data were available except for those from 4 subjects in WHO-FC II. For the above reasons, the effect of WHO-FC on the changes in PVRI was not identified in Studies AC-052-373 and AC-052-377. The mean change in PVRI in the subjects in WHO-FC I in Study AC-052-373 was -215.5 $dyn \cdot sec \cdot cm^{-5} \cdot m^2$. In Study 052-356, the mean change in the subjects in WHO-FC III was slightly smaller than that in the subjects in WHO-FC II, but the median changes were similar between the subjects in WHO-FC II and III (-275 and -268

dyn·sec·cm^{-5}·m^2, respectively). In these studies, there were no differences observed in changes in PVRI due to differences in WHO-FC. Based on the above, a difference in WHO-FC is considered unlikely to affect the changes in PVRI. In the Japanese and foreign clinical studies, improvement was also observed in WHO-FC and pulmonary hemodynamic parameters other than PVRI, regardless of baseline WHO-FC.

In the specified drug use-results survey for approved Tracleer Tablets 62.5 mg, 22.5% (23 of 102) of pediatric PAH patients aged <15 years with baseline WHO-FC IV improved to WHO-FC I, II, or III at Month 24. Approximately 74% of these 23 patients used other PAH drugs concomitantly at the start of treatment with bosentan, and concomitant drugs added after the start of bosentan therapy may have contributed to their improvement in WHO-FC status. Nevertheless, bosentan is expected to be effective even in pediatric PAH patients in WHO-FC IV.

A safety analysis was performed on adverse event data from the Japanese and foreign clinical studies. The incidences of adverse events by WHO-FC are shown in Table 25.

Table 25. Incidences of adverse events by WHO-FC in Japanese and foreign clinical studies

	Foreign clinical study [a]				Japanese clinical study [b]
WHO-FC (Number of subjects)	I (19)	II (65)	III (35)	IV (0)	II (n = 4)
Adverse events	68.4 (13)	73.8 (48)	62.9 (22)	–	75.0 (3)
Death	5.3 (1)	0 (0)	5.7 (2)	–	0 (0)
Serious adverse events	10.5 (2)	10.8 (7)	22.9 (8)	–	0 (0)
Adverse events for which a relationship to the study drug cannot be ruled out	15.8 (3)	35.4 (23)	17.1 (6)	–	25.0 (1)
Adverse events leading to discontinuation	5.3 (1)	1.5 (1)	11.4 (4)	–	0 (0)
Adverse events characteristic of bosentan					
Hepatic function abnormal	0 (0)	6.2 (4)	2.9 (1)	–	25.0 (1)
Anaemia	5.3 (1)	1.5 (1)	0.0 (0)	–	25.0 (1)
Oedema	0 (0)	3.1 (2)	5.7 (2)	–	0 (0)
Blood pressure decreased	0 (0)	1.5 (1)	0 (0)	–	0 (0)

% (number of subjects)
[a] Pooled data set of Studies AC-052-356, AC-052-365, and AC-052-373
[b] Study AC-052-377

The incidence of serious adverse events was 22.9% and slightly higher in patients with baseline WHO-FC III. All these events were assessed as unrelated to the study drug. There were no WHO-FC-associated differences in the incidences of other adverse events. The results of the Japanese and foreign clinical studies showed no major differences in the trend of occurrence of adverse events among patients in different WHO functional classes. For these reasons, treatment with bosentan is unlikely to raise safety concerns in patients with any PAH WHO-FC.

As shown above, patients in WHO-FC I, II, or III improved in PVRI and WHO-FC status. The safety profiles of bosentan did not markedly differ among these patients, and no specific issues were identified that might give rise to safety concerns. No patients in WHO-FC IV were enrolled in the Japanese or foreign clinical studies. However, in the specified drug use-results survey for Tracleer Tablets 62.5 mg, the proportion of patients in WHO-FC IV at 2 years after the start of bosentan therapy was decreased relative to baseline. Therefore, bosentan is expected to be effective in improving the pathological condition of PAH.

PAH is a progressive and fatal disease that cannot be completely cured without lung transplantation. Patients in WHO-FC IV are treated mainly with continuous intravenous therapy with epoprostenol sodium, but the therapy requires catheterization which is invasive and may cause infection. Also, the inconvenience of carrying an infusion bag makes many patients reluctant to receive this therapy. Consequently, in clinical practice, oral combination therapy is often administered to patients in WHO-FC IV wherever possible. In fact, the treatment algorithms for adult and pediatric pulmonary hypertension recommend continuous intravenous therapy with epoprostenol sodium and also advise considering the use of oral PAH drugs including bosentan for patients in WHO-FC IV (Galiè N *et al*., *J Am Coll Cardiol*. 2013;62:D60-72; Ivy DD *et al*., *J Am Coll Cardiol*. 2013;62:D117-126). Based on the above, the applicant considers that the pediatric formulation of bosentan should be indicated for "pulmonary arterial hypertension" regardless of WHO-FC status.

In light of the fact that bosentan for adults is indicated for "pulmonary arterial hypertension in patients in WHO Functional Class II, III or IV," PMDA asked the applicant to justify why the proposed indication of bosentan for pediatric use covers a wider range of patients including those in WHO-FC I.

The applicant's response:
The ultimate goals in treating PAH patients are to control the disease with oral agents before it becomes life-threatening or requires continuous intravenous therapy with epoprostenol sodium and to improve WHO-FC III and IV patients to FC I or II and to improve all FC II patients to FC I or at least to maintain FC II in patients presenting in that FC (Barst RJ *et al*., *J Am Coll Cardiol*. 2009;54:S78-84). Therefore, it is crucial to initiate treatment with oral agents aggressively when PAH is diagnosed even in asymptomatic patients at an early stage of WHO-FC I. While PAH is histopathologically and pathophysiologically similar in adults and children, the disease may progress more rapidly with a poorer prognosis in children than in adults (Sandoval J *et al*., *J Am Coll Cardiol*. 1995;25:466-474; van Loon RL *et al*., *Circulation*. 2011;124:1755-1764). Therefore, the goal of treating pediatric PAH patients should be set higher than that for adult patients (Fukushima H. *Biomedicine & Therapeutics*. 2010;44:852-856), and aggressive treatment should be started in pediatric patients. Patients in WHO-FC I accounted for 29.6% (19 of 64) of patients enrolled in Study AC-052-373. Two of the 19 subjects in WHO-FC I were evaluated for pulmonary hemodynamics at Week 12 and showed decreases in PVRI from baseline at Week 12. Furthermore, Of the 19 subjects in WHO-FC I, 18 (94.7%) remained unchanged at Week 24, indicating favorable results. Accordingly, bosentan is expected to be effective

also for treating pediatric PAH patients in WHO-FC I. Based on the above, the applicant considers it appropriate to propose that the pediatric formulation of bosentan should be indicated for "pulmonary arterial hypertension," irrespective of WHO-FC, covering a wider range of patients than that for adults.

PMDA's view:
In the Japanese and foreign clinical studies, evaluable hemodynamic data were available from 2 subjects in WHO-FC I, 19 subjects in WHO-FC II, and 4 subjects in WHO-FC III. No subjects in WHO-FC IV were enrolled in the studies or evaluated for PVRI. In Studies AC-052-373 and AC-052-377, it was difficult to evaluate PVRI in subjects in WHO-FC II or III because of the small number of the patients enrolled in these studies. However, in Study AC-052-356, which enrolled the largest number of subjects evaluable for PVRI, both WHO-FC II and III subgroups showed decreases in PVRI after administration of bosentan. No marked difference was seen in the safety profiles between these subgroups in the Japanese and foreign clinical studies. Based on the above, PMDA considers that bosentan has been demonstrated to be safe and effective in patients in WHO-FC II or III to an extent that the clinical use of the product in the patient populations is acceptable.

Patients in WHO-FC I are asymptomatic and often come to medical attention later in the disease process, and an accurate diagnosis of PAH is difficult for physicians who are not specialists in this field. For these reasons, only a small number of PAH patients in WHO-FC I were enrolled in the studies. Under such circumstances, it was difficult to evaluate hemodynamics in this patient population, which is understandable. However, PVRI improved in the subjects in Study AC-052-373, which evaluated only a very small number of subjects. Of 64 subjects enrolled, 19 (29.6%) were in WHO-FC I, and 18 of the 19 subjects in WHO-FC I remained stable. In light of the above findings, PMDA considers that bosentan is expected to be effective also in patients in WHO-FC I.

Since no patients in WHO-FC IV were enrolled in the Japanese or foreign studies in pediatric PAH patients, it is difficult to evaluate the efficacy and safety of bosentan in this patient population based on the results of the clinical studies. However, PAH is a fatal progressive disease. For adult PAH patients, the initiation of aggressive treatment at an early stage of the disease has been recommended, and combination therapy with drugs with different mechanisms of action selected from PGI_2 preparations, ERAs, and PDE-5 inhibitors or soluble guanylate cyclase stimulators has been suggested for serious cases or patients with poor response to monotherapy. This treatment policy should also be applicable to pediatric PAH patients. Furthermore, WHO-FC fluctuates with changes in the treatment or pathological conditions of patients, and currently there are no PAH drugs approved for pediatric dosing regimens in Japan. In light of the above and other considerations, PMDA considers it clinically meaningful to provide bosentan, a drug with confirmed efficacy in patients in WHO-FC II and III, as a therapeutic option for pediatric PAH patients in WHO-FC IV, which is a more serious condition.

Based on the above, PMDA considers that bosentan can be indicated for all pediatric PAH patients, regardless of WHO-FC status. Nevertheless, PMDA will make a final decision on the indication of the

pediatric formulation of bosentan and the information that should be included in the package insert, taking account of comments from the Expert Discussion.

4.(iii).B.(5).2) Etiology

PMDA asked the applicant to explain the efficacy and safety of bosentan for each etiology of PAH in the Japanese and foreign clinical studies in pediatric PAH patients (Studies AC-052-356, AC-052-365, AC-052-373, and AC-052-377) and then to justify why the applicant proposed that the pediatric formulation of bosentan should be indicated for "pulmonary arterial hypertension," irrespective of etiology, covering also patients excluded from the clinical studies.

The applicant's response:

The changes in PVRI by etiology of PAH in the Japanese and foreign clinical studies in pediatric PAH patients are shown in Table 26.

Table 26. Change in PVRI from baseline by etiology of PAH in Japanese and foreign clinical studies ($dyn \cdot sec \cdot cm^{-5} \cdot m^2$)

Etiology of PAH	I/H PAH	CHD PAH
AC-052-356 [a]		
Number of subjects	10	7
Mean ± SD	-345.8 ± 400.2	-233.4 ± 720.5
(95% CI)	(-632.1, -59.5)	(-899.8, 433.0)
AC-052-373 [b]		
Number of subjects	1	3
Mean ± SD	0	-143.6 ± 163.1
(95% CI)	–	(-548.9, 261.6)
AC-052-377 [a]		
Number of subjects	5	1
Mean ± SD	-9.2 ± 288.8	22
(95% CI)	(-367.8, 349.4)	–

Analysis populations: all enrolled patients in Study AC-052-356, all-randomized set in Study AC-052-367, and PPS in Study AC-052-377.
I/H PAH, idiopathic or heritable PAH; CHD PAH, PAH associated with congenital heart disease.
[a] Change from baseline to Week 12
[b] Change from baseline to Week 24

In Study AC-052-356, PVRI tended to decrease after administration of bosentan in all patient subgroups of idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease, showing no effect of etiology of PAH on PVRI. Only 1 subject with idiopathic or heritable PAH was enrolled in Study AC-052-373 and 1 subject with PAH associated with congenital heart disease in Study AC-052-377. Neither study clarified the effect of etiology of PAH on PVRI. The PVRI in the subjects with PAH associated with congenital heart disease in Study AC-052-373 and in the subjects with idiopathic or heritable PAH in Study AC-052-377 tended to decrease after administration of bosentan. These results can be interpreted as showing that the etiology of PAH is unlikely to affect the change in PVRI after administration of bosentan. In addition to PVRI, WHO-FC status and pulmonary hemodynamics improved regardless of the etiology of PAH in subjects in the Japanese and foreign clinical studies.

The incidences of adverse events by etiology of PAH in the Japanese and foreign clinical studies are shown in Table 27.

Table 27. Incidences of adverse events by etiology of PAH in Japanese and foreign clinical studies

	Foreign clinical study [a]		Japanese clinical study [b]	
	I/H PAH (n = 77)	CHD PAH (n = 41)	I/H PAH (n = 5)	CHD PAH (n = 1)
Adverse events	67.5 (52)	73.2 (30)	80.0 (4)	100.0 (1)
Death	2.6 (2)	2.4 (1)	0 (0)	0 (0)
Serious adverse events	15.6 (12)	9.8 (4)	20.0 (1)	0 (0)
Adverse events for which a causal relationship to the study drug cannot be ruled out	31.2 (24)	19.5 (8)	20.0 (1)	0 (0)
Adverse events leading to study drug discontinuation	5.2 (4)	4.9 (2)	0 (0)	0 (0)
Adverse events characteristic of bosentan				
Hepatic function abnormal	3.9 (3)	4.9 (2)	20.0 (1)	0 (0)
Anaemia	1.3 (1)	2.4 (1)	20.0 (1)	0 (0)
Oedema	3.9 (3)	2.4 (1)	0 (0)	0 (0)
Blood pressure decreased	1.3 (1)	0 (0)	0 (0)	0 (0)

% (number of subjects)
I/H PAH, idiopathic or heritable PAH; CHD PAH, PAH associated with congenital heart disease.
[a] Pooled data set of Studies AC-052-356, AC-052-365, and AC-052-373
[b] Study AC-052-377

The incidence of overall serious adverse events was slightly higher in subjects with idiopathic or heritable PAH than in those with PAH associated with congenital heart disease, but the occurrence of serious adverse events assessed as related to the study drug was comparable between the subgroups: 2 subjects with idiopathic or heritable PAH (tachycardia, hypertension, tremor, and dizziness in 1 subject and pulmonary arterial hypertension in 1 subject) and 1 subject with PAH associated with congenital heart disease (hepatic function abnormal). While the incidence of adverse events a causal relationship to the study drug could not be ruled out was slightly higher in subjects with idiopathic or heritable PAH than in those with PAH associated with congenital heart disease, there were no differences by etiology of PAH in the incidences of adverse events leading to study drug discontinuation and adverse events of hepatic function abnormal, anemia, edema, and blood pressure decreased. Taking into account the fact that no marked difference was found in occurrence of adverse events among patients with PAH of different etiologies, the applicant considers that the use of bosentan in the treatment of PAH is unlikely to pose safety concerns in patients with any etiology of PAH.

As stated above, the results of the clinical studies demonstrated that there are no marked differences in the efficacy and safety of bosentan between patients with idiopathic or heritable PAH and those with PAH associated with congenital heart disease. Meanwhile, no data were available on the efficacy or safety of bosentan in patients with PAH of other etiologies, such as PAH associated with HIV infection, drug- or toxin-induced PAH, and PAH associated with connective tissue disease. Pediatric PAH is pathologically similar to adult PAH except that the former progresses more rapidly with a poorer prognosis than the latter (Sandoval J *et al*., *J Am Coll Cardiol*. 1995;25:466-474; van Loon RL *et al*.

Circulation. 2011;124:1755-1764). According to the guidelines of the American College of Cardiology revised at the Fifth World Symposium on Pulmonary Hypertension (Simonneau G *et al*. *J Am Coll Cardiol*. 2013;62:D34-41) and the Japanese Guidelines for Treatment of Pulmonary Hypertension (revised version, 2012), diseases with common features of PAH are classified into Group 1 of the clinical classification of pulmonary hypertension. The guidelines of the American College of Cardiology imply that PAH classification is common for children and adults (Simonneau G *et al*., *J Am Coll Cardiol*. 2013;62:D34-41) and recommend bosentan for PAH (Group 1) (Galiè N *et al*. *J Am Coll Cardiol*. 2013;62:D60-72). Therefore, the applicant considers it appropriate to propose that bosentan should be indicated for "pulmonary arterial hypertension" representing Group 1 of the clinical classification in the guidelines of the American College of Cardiology, regardless of etiology of PAH.

However, the Japanese and foreign clinical studies did not yield data that support the efficacy and safety of bosentan in patients with PAH associated with HIV infection, drug- or toxin-induced PAH, or PAH associated with connective tissue disease, which are included in the Group 1 in the guidelines of the American College of Cardiology (Simonneau G *et al*., *J Am Coll Cardiol*. 2013;62:D34-41). Furthermore, a post-marketing surveillance (PMS) of bosentan was conducted in Europe in 146 pediatric PAH patients aged 2 to 11 years, and the PMS included only 4 patients with PAH associated with HIV infection, drug- or toxin-induced PAH, or PAH associated with connective tissue disease (Beghetti M *et al*., *Pediatr Res*. 2008;64:200-204). Other published literature has also reported that cases of pediatric PAH of such etiologies are very rare (Beghetti M *et al*., *Eur Respir Rev*. 2014;23:498-504). Therefore, the efficacy and safety of bosentan in patients with these etiologies of PAH have not been clarified. Taking the above into account, the applicant proposes that the following precautionary statement should be included in the "Precautions for Indication" section of the package insert: "The efficacy and safety of bosentan have not been established in patients with PAH other than idiopathic or heritable PAH, or PAH associated with congenital heart disease."

PMDA's view:

At the Fifth World Symposium on Pulmonary Hypertension, etiologies of pediatric PAH, along with those of adult PAH, were discussed based on the Nice classification (Ivy DD *et al*. *J Am Coll Cardiol*. 2013;62:D117-126), and despite the fact that the proportion of etiologies of PAH in children is quite different from that of adults, similar diagnostic approaches were proposed for adult and pediatric PAH. Since PAH is a rare disease and is even rarer in children, it is understandable that there are difficulties in conducting any clinical studies in pediatric patients with PAH other than idiopathic or heritable PAH and PAH associated with congenital heart disease that have been investigated in the clinical studies (i.e., PAH associated with connective tissue disease or other underlying diseases). The results of the Japanese and foreign clinical studies suggest that the efficacy and safety of bosentan in patients with idiopathic or heritable PAH and those with PAH associated with congenital heart disease, which are major etiologies of PAH in Group 1, are similar irrespective of the etiologies. The Japanese and foreign guidelines, including the latest treatment algorithm for adult PAH, recommend some therapies common for overall patients with PAH of different etiologies in Group 1. This is based on a common

understanding that patients with PAH, regardless of etiology, may benefit from these therapies. Therapies for individual pediatric PAH patients are determined based on the results of large-scale clinical studies in adult PAH patients, and treatment algorithms for pediatric PAH do not include information on therapies recommended for each etiology of PAH. Given this background, PMDA considers it acceptable that the pediatric formulation of bosentan is indicated for "pulmonary arterial hypertension," irrespective of etiology, including PAH types which are difficult to examine in a clinical study setting and that the following precautionary statement is included in the "Precautions for Indication" section of the package insert: "The efficacy and safety of bosentan have not been established in patients with PAH other than idiopathic or heritable PAH, or PAH associated with congenital heart disease."

4.(iii).B.(6) Dosage and administration

4.(iii).B.(6).1) Rationale for dosage and administration

PMDA asked the applicant to provide the rationales for the dosing regimens (initial dose, maintenance dose) employed in the foreign clinical studies (AC-052-356, AC-052-365, and AC-052-373) and then to explain the rationales for the approved dosing regimen for pediatric PAH patients in Europe, the dosing regimens used in the Japanese clinical studies, and the proposed dosing regimen in Japan.

The applicant's response:

In both Japan and other countries, the approved dosing regimen for Tracleer Tablets 62.5 mg is an initial dose of 62.5 mg b.i.d. for 4 weeks that is followed by a maintenance dose of 125 mg b.i.d., except that dose escalation up to 250 mg/day on an as-needed basis is allowed in Japan. The above maintenance dose is equivalent to 2.08 mg/kg/dose with an assumption of an adult body weight of 60 kg. [redacted] In this study, the steady-state AUC_{τ} of bosentan in pediatric patients was lower than that in adult patients [see "4.(ii).B.(2) Effects of age on the pharmacokinetics of bosentan"]. In Study AC-052-365 using the new pediatric formulation, bosentan was to be administered at an initial dose of 2 mg/kg b.i.d. for 4 weeks and then to be increased to the maintenance dose of 4 mg/kg b.i.d. Patients weighing ≥30 kg were to receive an initial dose of 64 mg/dose and a maintenance dose of 120 mg/dose in order to avoid exceeding the maximum maintenance dose of 125 mg/dose for adults. However, AUC_{τ} in pediatric patients receiving the 4 mg/kg b.i.d. dose remained lower than that in adult patients, and the exposure to bosentan with this regimen was not higher than that at a dose of 2 mg/kg b.i.d. [see "4.(ii).A.(2).2) Study AC-052-365 (Attached document, 5.3.3.2.2)"]. Study AC-052-373 was designed on the basis of these results, and bosentan was administered at 2 mg/kg b.i.d. and t.i.d. In this study, however, the exposure did not increase with the increase of dosing frequency [see "4.(ii).A.(2).3) Study AC-052-373 (Attached document, 5.3.3.2.3)"]. As shown above, since the exposure to bosentan did not increase with dose escalation from 2 mg/kg b.i.d. to 4 mg/kg b.i.d. or the increase of dosing frequency from 2 mg/kg b.i.d. to 2 mg/kg t.i.d., the exposure to bosentan in pediatric PAH patients was predicted to reach a plateau after administration at

2 mg/kg b.i.d. The 2 mg/kg b.i.d. dose did not produce marked differences in exposure to bosentan in Studies AC-052-356, AC-052-365, and AC-052-373, and PVRI improved in Studies AC-052-356 and AC-052-373 without no significant safety problems. Accordingly, the dosing regimen of 2 mg/kg b.i.d. was eventually selected for pediatric PAH patients in Europe. Based on the results of Studies AC-052-365 and AC-052-373 showing that the exposure to bosentan in pediatric patients receiving the 2 mg/kg b.i.d. dose was lower than that in adult patients, it is recommended that bosentan should be administered at 2 mg/kg b.i.d. from the start of the therapy and should be maintained at the dose.

In light of the results of Study AC-052-365, bosentan was to be started and maintained at 2 mg/kg b.i.d., which is the dosing regimen approved in Europe, in the Japanese Study AC-052-377. The clinical study of the pediatric formulation of bosentan was conducted with the maximum dose of 120 mg/dose which did not exceed the maximum dose (125 mg/dose) for adult patients. While AUC_{τ} at the steady state after repeated administration was slightly lower than the exposure in non-Japanese pediatric PAH patients in Studies AC-052-365 and AC-052-356 [see "4.(ii).B.(1) Differences in pharmacokinetics between Japanese and non-Japanese pediatric PAH patients"], the degree of improvement in pulmonary hemodynamic parameters in Study AC-052-377 was generally comparable to that in Study AC-052-356, suggesting that Japanese pediatric PAH patients would benefit from treatment with the pediatric dispersible tablets of bosentan administered at 2 mg/kg. The results of Studies AC-052-377 and AC-052-378 (the extension study of Study AC-052-377) showed no marked difference in the safety profiles of bosentan between Japanese pediatric and adult PAH patients, nor were any adverse events reported that were specific to pediatric PAH patients. Based on the above, the dosing regimen used in Study AC-052-377 was proposed as the recommended dosing regimen in Japan.

PMDA's view:
In Study AC-052-356, the efficacy and safety of bosentan at approximately 2 mg/kg b.i.d were evaluated in non-Japanese pediatric PAH patients. The results of Study AC-052-365 showed that the exposure to bosentan at a dose of 4 mg/kg b.i.d. was not higher than that at a dose of 2 mg/kg b.i.d. The results of Study AC-052-373 showed that the exposure to bosentan at a dose of 2 mg/kg t.i.d. was not higher than that at a dose of 2 mg/kg b.i.d. Based on these results, a dosing regimen of 2 mg/kg b.i.d was approved as the recommend starting and maintenance dosing regimen in Europe. In Japan, in light of the recommended dosing regimen in Europe and the similarities in pharmacokinetics of bosentan between Japanese and non-Japanese adult PAH patients, a clinical study (AC-052-377) was conducted with the same dosing regimen as approved in Europe. The study, though conducted in a small number of subjects, suggested that bosentan is effective also in Japanese patients [see "4.(iii).B.(3) Efficacy"] and showed no particular safety concerns [see "4.(iii).B.(4) Safety"]. Therefore, PMDA considers that the dosing regimen of bosentan for Japanese pediatric PAH patients should be 2 mg/kg b.i.d., the same dose as that for non-Japanese pediatric PAH patients.

4.(iii).B.(6).2) Age

Since the dosing regimen in the Summary of Product Characteristics of bosentan is recommended for children aged ≥1 year in Europe, PMDA asked the applicant to explain the efficacy and safety of bosentan by age in the Japanese and foreign clinical studies and then to discuss whether any minimum age limit should be set for patients in Japan.

The applicant's response:

The changes in PVRI by age in the Japanese and foreign clinical studies in pediatric PAH patients are shown in Table 28. PVRI was calculated in no subjects aged <1 year.

Table 28. Changes in PVRI from baseline by age in Japanese and foreign clinical studies (dyn·sec·cm^{-5}·m^2)

Age	1 to <2 years	2 to <7 years	7 to <15 years
AC-052-356 [a]			
Number of subjects	0	6	8
Mean ± SD	–	-568.5 ± 576	-290.3 ± 209.4
(95% CI)	–	(-1172.9, 35.9)	(-465.3, -115.2)
AC-052-373 [b]			
Number of subjects	0	1	3
Mean ± SD	–	0	-143.6 ± 163.1
(95% CI)	–	–	(-548.9, 261.6)
AC-052-377 [a]			
Number of subjects	1	3	2
Mean ± SD	-138	155.7 ± 193.9	-176.5[c]
(95% CI)	–	(-325.9, 637.2)	–

Analysis populations: all enrolled patients in Study AC-052-356, all-randomized set in Study AC-052-373, and PPS in Study AC-052-377.

[a] Change from baseline to Week 12

[b] Change from baseline to Week 24

[c] 53 dyn·sec·cm^{-5}·m^2 in 1 subject and -406 dyn·sec·cm^{-5}·m^2 in the other subject.

In Study AC-052-356, the decrease in PVRI tended to be greater in patients aged 2 to <7 years, but PVRI decreased in both age groups of 2 to <7 years and 7 to <15 years. In Study AC-052-373, the effect of age on the change in PVRI could not be identified because PVRI data for the age group of 2 to <7 years were available from only 1 subject; however, a decrease in PVRI was noted in subjects aged 7 to <15 years. In Study AC-052-377, while PVRI decreased in subjects aged 1 to <2 years and those aged 7 to <15 years, the change in PVRI from baseline (mean ± standard deviation) in subjects aged 2 to <7 years was 155.7 ± 193.9 dyn·sec·cm^{-5}·m^2, indicating an increase in PVRI. Although no improvement in PVRI was observed in subjects aged 2 to <7 years in Study AC-052-377, the applicant considers that there are no definite age-specific differences in the effect of bosentan on the change in PVRI when taking into account the small number of subjects evaluated in this study and the overall results of the 3 studies shown in Table 28.

A safety analysis was performed on adverse event data from the Japanese and foreign clinical studies. The incidences of adverse events by age are shown in Table 29.

Table 29. The incidences of adverse events by age in Japanese and foreign clinical studies

Age	<1 year	1 to <2 years	2 to <7 years	7 to <15 years
Foreign clinical studies [a]				
Number of subjects	6	15	45	50
Adverse events	83.3 (5)	60.0 (9)	73.3 (33)	66.0 (33)
Death	16.7 (1)	6.7 (1)	0 (0)	2.0 (1)
Serious adverse events	66.7 (4)	13.3 (2)	11.1 (5)	12.0 (6)
Adverse events for which a causal relationship to the study drug cannot be ruled out	0 (0)	0 (0)	31.1 (14)	34.0 (17)
Adverse events leading to study drug discontinuation	16.7 (1)	6.7 (1)	2.2 (1)	6.0 (3)
Adverse events characteristic of bosentan				
Hepatic function abnormal	0 (0)	0 (0)	2.2 (1)	8.0 (4)
Anaemia	0 (0)	0 (0)	2.2 (1)	2.0 (1)
Oedema	0 (0)	0 (0)	2.2 (1)	4.0 (2)
Blood pressure decreased	0 (0)	0 (0)	0 (0)	2.0 (1)
Japanese clinical study [b]				
Number of subjects	0	1	3	2
Adverse events	0 (0)	100.0 (1)	100.0 (3)	50.0 (1)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events	0 (0)	100.0 (1)	0 (0)	0 (0)
Adverse events for which a causal relationship to the study drug cannot be ruled out	0 (0)	0 (0)	33.3 (1)	0 (0)
Adverse events leading to study drug discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events characteristic of bosentan				
Hepatic function abnormal	0 (0)	0 (0)	33.3 (1)	0 (0)
Anaemia	0 (0)	0 (0)	33.3 (1)	0 (0)
Oedema	0 (0)	0 (0)	0 (0)	0 (0)
Blood pressure decreased	0 (0)	0 (0)	0 (0)	0 (0)

% (number of subjects)
[a] Pooled data set of Studies AC-052-356, AC-052-365, and AC-052-373
[b] Study AC-052-377

In the foreign clinical studies, the overall incidence of adverse events in subjects aged <1 year was 83.3%, which was slightly higher than that in all age groups combined (69.0%). However, the relationship of age to the incidence of adverse events could not be clarified because safety data for the age group of <1 year were available from only 6 subjects. There were no other age-specific differences in safety profiles.

In the clinical development program of bosentan in Europe, Studies AC-052-356, AC-052-365, and AC-052-367 enrolled pediatric PAH patients aged ≥2 years, while the subsequent study, AC-052-373, was conducted in pediatric PAH patients aged ≥3 months to evaluate the efficacy and safety of bosentan also in patients aged <2 years. As a result, 21 subjects aged <2 years were enrolled in Study AC-052-373 and they accounted for 33% of the 64 study subjects. Meanwhile, 6 subjects aged <1 year were enrolled in the study, accounting for only 9.4% of the 64 study subjects. Consequently, the European authority concluded that the study failed to provide sufficient evidence to support recommending the same dosing

regimen for both patients aged ≥1 year and those aged <1 year. Finally, in Europe, the dosing regimen of 2 mg/kg b.i.d. was approved for the use in pediatric patients aged ≥1 year.

Clinical experience with bosentan in pediatric patients aged <1 year is limited because no subjects in this age group were enrolled in the Japanese or foreign clinical studies, except for 6 subjects in Study AC-052-373. However, in 5 of the 6 patients WHO-FC improved or remained unchanged from baseline at Week 24, and thus bosentan is expected to be effective in PAH patients aged <1 year. Serious adverse events were reported in 4 subjects aged <1 year in Study AC-052-373 (cardiac failure, disease progression, infection, metabolic disorder, and multi-organ failure in 1; respiratory distress in 1; oxygen saturation decreased, body temperature increased, pyrexia, and gastroenteritis in 1; atrial septal defect repair in 1), but a causal relationship to the study drug was ruled out for all these events. In Study AC-052-391, bosentan was administered to 13 patients with PPHN with a mean age of 1.9 days, and no clinically significant adverse events occurred in any of the subjects. These results can be interpreted as showing that bosentan is unlikely to pose any safety concerns when used in pediatric PAH patients aged <1 year. In the treatment of pediatric PAH patients, early intervention is crucial to improve their outcomes. Therefore, although PAH is difficult to be diagnosed in infants aged <1 year, treatment should be started as early as possible after a diagnosis of PAH is confirmed in patients in this age group.

Based on the above findings and the fact that no major age-specific differences in the efficacy and safety of bosentan were observed in the Japanese or foreign clinical studies, the applicant considers that bosentan can be used also in patients aged <1 year. However, since the youngest patient in the clinical studies was 0.3 years old, pediatric patients aged ≥28 days are thus considered to be eligible for treatment with bosentan. Bosentan should not be used in neonates because of a lack of clinical experience in this patient population. Therefore, the applicant considers that the wording of "infants and children" should be used in the "Dosage and Administration" section of the package insert to restrict the treatment with bosentan to patients aged ≥28 days. In addition, the applicant proposes that the "Precautions for Use" section of the draft package insert incude a precautionary statement to the effect that there is no clinical experience with bosentan in neonates and low-birth-weight infants.

PMDA's view:
Although only limited inferences can be drawn from the results of the Japanese and foreign clinical studies conducted in small numbers of subjects, the efficacy of bosentan in pediatric PAH patients aged ≥2 years has been generally demonstrated on the basis of improvement in PVRI. The results showed no major differences in age-specific safety profiles among patients aged ≥1 year.

One and 15 subjects aged 1 to <2 years were enrolled in Studies AC-052-377 and AC-052-373, respectively. Hemodynamic evaluation was available in only the subject in Study AC-052-377, in whom PVRI improved with a change of -138 $dyn \cdot sec \cdot cm^{-5} \cdot m^2$ from baseline to Week 12. In Study AC-052-373, WHO-FC improved in 3 of 15 subjects and remained unchanged in 11 of 15 subjects, as assessed

by changes from baseline to Week 24, showing clinical stability in WHO-FC. These results can be interpreted as showing a certain degree of efficacy of bosentan in PAH patients aged 1 to <2 years.

Study AC-052-373 enrolled 6 subjects aged <1 year. Although hemodynamics could not be evaluated in the 6 subjects, an assessment of the changes in WHO-FC from baseline to Week 24 showed that WHO-FC improved in 1 subject and remained unchanged in 4 subjects, indicating clinical stability in WHO-FC. Among safety findings, the incidence of overall adverse events in subjects aged <1 year was 83.3%, which was higher than the incidence in all age groups combined (69.0%). Four subjects experienced serious adverse events, all of which were assessed as unrelated to study treatment. The predominance of PAH associated with congenital heart disease among pediatric PAH patients suggests an early age of onset, and there are patients who can be rendered operable by early initiation of appropriate treatment or whose outcome can be improved by postoperative PAH management. In view of the above, the pediatric formulation of bosentan can be a therapeutic option if the package insert includes a precautionary statement to the effect that the efficacy and safety in patients aged <1 year have not been established. PMDA considers it appropriate to restrict the use of bosentan to the treatment of PAH in infants and children and to provide precautions against the use in low-birth-weight infants or neonates because no neonates received bosentan in the Japanese or foreign clinical studies.

PMDA will finalize its decision on the use in patients aged <1 year and the details of the statements in the package insert, taking into account the comments from the Expert Discussion.

4.(iii).B.(7) Post-marketing investigations

The applicant's explanation on its post-marketing investigations:

Because of the limited number of subjects evaluated in the Japanese clinical study (AC-052-377), the applicant plans to conduct a specified drug use-results survey (with an observation period of 1 year) to investigate the efficacy and safety of the pediatric formulation of bosentan in all treated patients in clinical practice (planned sample size, 120 patients for safety analysis).

Hepatic function disorders and hematology test results will be investigated with high priority in the survey.

The sample size was determined as follows:

The number of pediatric PAH patients aged <15 years were estimated to be 331 by multiplying 2587, the number of PAH patients determined from the number of holders of a Certificate of Recipient of Medical Treatment of Designated Diseases at the end of fiscal 2013, by 12.8%, the proportion of children aged <15 years in the overall population as of April 1, 2014 (data from the Population Estimates issued by the Statistics Bureau, Ministry of Internal Affairs and Communications). An overseas epidemiological study on treatment of pediatric PAH reported that ERAs were prescribed for 43% of pediatric PAH patients (Barst R.J *et al*., *Circulation*. 2012;125:113-122). Based on the above data, 85 existing pediatric PAH patients were estimated to receive the pediatric formulation of bosentan with an

assumption that ERA therapy would be switched to bosentan in approximately 60% of existing pediatric PAH. The number of holders of a Certificate of Recipient of Medical Treatment of Designated Disease increased by 1027 during 3 years between 2011 and 2013 with an average annual increase of 342 patients, and, based on the data, the annual increase in the number of pediatric patients with newly diagnosed PAH receiving ERAs was estimated to be approximately 19. Then, it was assumed that bosentan would be indicated in >60% of pediatric patients with newly diagnosed PAH on ERAs each year, i.e., bosentan would be used in a higher percentage of pediatric patients with newly diagnosed PAH as compared with existing pediatric patients. With the assumption, it was estimated that 40 pediatric patients with newly diagnosed PAH would receive the pediatric formulation of bosentan during the enrollment period of the survey (i.e., 3 years and 6 months). Finally, the sample size was determined to be 125 patients (120 for safety analysis).

Serious liver function test abnormal is an important risk associated with bosentan therapy, and its incidence was 3.4% in the pooled data set of the foreign clinical studies. An analysis with a statistical power of 95% can detect at least 1 case of such event in the safety analysis population of 120 patients.

PMDA's view:
Because of the very limited number of Japanese patients enrolled in the clinical studies, the post-marketing surveillance should be conducted as a specified drug use-results survey covering all patients treated with the pediatric formulation of bosentan in order to aggressively and immediately collect and provide information on the efficacy and safety of bosentan and the occurrence of adverse events including hepatic function disorder, anemia, hemoglobin decreased, and platelets decreased in routine clinical practice. PMDA will finalize its decision on the details of the post-marketing surveillance after a discussion with expert advisors in the Expert Discussion on the topics including the appropriateness of the identified safety specifications, risk classification, pharmacovigilance activities, and risk minimization activities in accordance with the Risk Management Plan Guidance (Notification No. 0411-1 of the Safety Division, PFSB and Notification No. 0411-2 of the Evaluation and Licensing Division, PFSB, dated April 11, 2012).

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

The inspections are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, PMDA has concluded that the efficacy of bosentan in the treatment of pediatric PAH has been demonstrated and that its safety is acceptable in view of its observed benefits. The product is expected to offer a new therapeutic option for the treatment of pediatric PAH and is therefore considered of clinical significance. PMDA considers that a further review is needed for issues

including the intended patient populations, indication, dosage and administration, details of precautionary statements in the package insert, and post-marketing investigations.

PMDA considers that the application may be approved if the product is not considered to have any particular problems based on the comments from the Expert Discussion.

Review Report (2)

August 17, 2015

I. Product Submitted for Registration

[Brand name]	Tracleer Pediatric Dispersible Tablets 32 mg
[Non-proprietary name]	Bosentan Hydrate
[Applicant]	Actelion Pharmaceuticals Japan Ltd.
[Date of application]	March 31, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

PMDA concluded that although it is difficult to evaluate the efficacy of Tracleer Pediatric Dispersible Tablets 32 mg (hereinafter referred to as the "pediatric formulation") only based on the results of the Japanese phase III study (AC-052-377) in pediatric patients with pulmonary arterial hypertension (PAH), the pediatric formulation is expected to be effective in Japanese pediatric PAH patients, taking into account the following findings: (1) The efficacy of the pediatric formulation was demonstrated in a small but definite number of subjects in Study AC-052-377; (2) the efficacy of bosentan hydrate (hereinafter referred to as "bosentan"), as assessed by changes in hemodynamics and WHO functional class status, was demonstrated in foreign clinical studies in pediatric PAH patients; (3) the efficacy of bosentan has been established in Japanese adult patients; and (4) there are no differences in pathology or treatment of PAH between adults and children. The above PMDA's conclusion was supported by the expert advisors.

(2) Safety

The expert advisors commented that the necessity of precautionary statements regarding the risk of QT interval prolongation should be discussed, because some subjects had Fridericia's formula-corrected QT (QTcF) interval >450 ms and increases in QTcF interval of >30 ms in the foreign clinical studies in pediatric PAH patients. Accordingly, PMDA asked the applicant to discuss the necessity of precautionary advice regarding this matter, taking into account the currently available data from Japanese and foreign clinical studies in adult and pediatric PAH patients and the post-marketing experience.

The applicant's response:

In foreign clinical studies in pediatric PAH patients (Studies AC-052-356, AC-052-365, and AC-052-373), 7 subjects had increases in QTcF interval to >450 ms and of >30 ms over baseline, and an adverse event related to QT interval prolongation (electrocardiogram QT prolonged) was reported in 1 of the 7 subjects. Although a causal relationship between the event and the study drug could not be ruled out, the event was mild in severity and required no actions such as dose adjustment of the study drug. The event was reported to have resolved during the subsequent extension study period. The other 6 subjects had no adverse events related to QT interval prolongation such as torsade de pointes (TdP). Based on the above, the applicant considers that the QTcF prolongation observed in these subjects in foreign clinical studies is clinically insignificant.

The changes in QTcF in the Japanese and foreign clinical studies in adult and pediatric PAH patients are shown in Table 30.

Table 30. Changes in QTcF from baseline to the end of study in Japanese and foreign clinical studies in adult and pediatric PAH patients

	Adult patients			Pediatric patients	
	Foreign study		Japanese study	Foreign study	Japanese study
	Placebo	Bosentan	Bosentan	Bosentan	Bosentan
Number of subjects	66 [a]	138 [b]	40 [c]	110 [d]	6 [e]
Increase in QTcF interval of >30 ms over baseline	13.6 (9)	12.3 (17)	20.0 (8)	18.2 (20)	0 (0)
Increase in QTcF interval of >60 ms over baseline	4.5 (3)	4.3 (6)	0 (0)	5.5 (6)	0 (0)
Maximum QTcF interval of >450 ms to ≤480 ms	13.6 (9)	12.3 (17)	7.5 (3)	5.5 (6)	0 (0)
Maximum QTcF interval of >480 ms to ≤500 ms	1.5 (1)	4.3 (6)	0 (0)	2.7 (3)	0 (0)
Maximum QTcF interval of >500 ms	1.5 (1)	1.4 (2)	2.5 (1)	0.9 (1)	0 (0)

% (number of subjects)
[a] Placebo group in the AC-052-352 study
[b] Pooled data set of bosentan groups in Study AC-052-352
[c] Pooled data set of Studies AC-052-363 and AC-052-372
[d] Pooled data set of Studies AC-052-356, AC-052-365, and AC-052-373
[e] Pooled data set of Studies AC-052-377 and AC-052-378

In the Japanese clinical studies in pediatric PAH patients, no subjects presented with QTcF prolongation (increase in QTcF interval of >30 ms over baseline or to >450 ms). No marked difference in proportion of subjects having QTcF prolongation was observed between the foreign clinical studies in pediatric PAH patients and the Japanese clinical studies in adult PAH patients. In the foreign clinical study in adult PAH patients (Study AC-052-352), the incidence of QTcF prolongation was comparable between the bosentan and placebo groups. Furthermore, the safety data obtained from the Japanese and foreign clinical studies in adult and pediatric PAH patients and the post-marketing experience show no marked differences in the trend of occurrence of adverse events related to QT interval prolongation, such as TdP, between adult and pediatric patients.

A non-clinical study in rabbit Purkinje fibers demonstrated that bosentan has no effects on maximum rate of depolarization or early afterdepolarization.

Based on the above, the applicant considers that the bosentan has a low risk of QT interval prolongation when used in pediatric PAH patients and that hence there is no need to provide a precautionary statement regarding this risk in the package insert for children as well as adults.

PMDA's view:
In Study AC-052-352, increases in QTcF interval of >60 ms over baseline or to >500 ms and other clinically significant QT interval prolongation were observed in both the bosentan and placebo groups. In the foreign clinical studies in pediatric PAH patients, subjects experiencing QT interval prolongation included those with a left bundle branch block or an intraventricular conduction defect on electrocardiography (ECG). Therefore, it should be noted that some cases of QT interval prolongation observed in adult and pediatric patients treated with bosentan were attributable to factors other than bosentan, such as underlying cardiac diseases and concomitant drugs.

There is no strong evidence suggesting that the risk of bosentan-induced QT interval prolongation is significantly higher in children than in adults, because no specific difference in the trend of occurrence of adverse events related to QT interval prolongation, such as TdP and changes in QTcF, was found between adults and children in the Japanese or foreign clinical studies and because exposure to bosentan is unlikely to be substantially higher in children than in adults. At present, therefore, PMDA has concluded that it is unnecessary to provide any precautionary statement regarding the risk of QT interval prolongation in the package insert. However, the number of pediatric PAH patients evaluated in the Japanese and foreign clinical studies was very limited, and thus the risk of QT interval prolongation cannot be completely ruled out in children treated with bosentan. Therefore, further information on QT interval prolongation should be collected through post-marketing surveillance or by other means, and appropriate measures should be taken on the basis of the data collected.

Based on the above, PMDA asked the applicant to formulate a post-marketing surveillance plan in which patients would be monitored by ECG on a regular basis in order to collect information relevant to QT interval prolongation. The applicant properly addressed the issue.

On the basis of the above discussion, PMDA has concluded that safety information should be collected on the risk of QT interval prolongation in pediatric PAH patients in the post-marketing setting; and that however, the same precautionary statements as those in the package insert of the approved Tracleer Tablets 62.5 mg are sufficient to ensure that appropriate measures are taken for children in clinical practice, because there is no marked difference in safety profiles of bosentan, including types of adverse events, between adult and pediatric PAH patients. The above PMDA's conclusions were supported by the expert advisors. The expert advisors also supported PMDA's conclusion that the pediatric formulation of bosentan should be prescribed by a physician with adequate knowledge and experience

in the treatment of pediatric PAH because the duration of treatment with bosentan is expected to be longer in pediatric patients than in adult patients. Consequently, PMDA advised the applicant to include the following precautionary statement in the "Precautions for Indication" section of the package insert: "Use of the product should be considered in patients judged to be eligible by a physician with sufficient knowledge and experience in the treatment of pediatric PAH." The applicant addressed the issue properly.

(3) Indication

The pediatric formulation of bosentan was proposed to be used for treatment of "pulmonary arterial hypertension" regardless of etiology or WHO functional class status, and PMDA concluded that the proposed indication was acceptable. The PMDA's conclusion was supported by the expert advisors. The applicant proposed that the "Precautions for Indication" section of the package insert would include the following precautionary advice on the etiologies of PAH for which the efficacy and safety of bosentan have not been evaluated: "The efficacy and safety of the product have not been established in patients with PAH etiologies other than idiopathic or heritable PAH, or PAH associated with congenital heart disease." PMDA concluded the applicant's proposal was appropriate, and the PMDA's conclusion was supported by the expert advisors.

(4) Dosage and administration

At a meeting of the Exert Discussion, the expert advisors discussed the use of bosentan in PAH patients aged <1 year and, as a result, supported the following PMDA's conclusion: it is meaningful to provide the pediatric formulation of bosentan as a therapeutic option for PAH patients aged <1 year, provided that the "Precautions for Dosage and Administration" section of the package insert includes a precautionary statement to the effect that the efficacy and safety of bosentan in patients aged <1 year have not been established. The applicant proposed that because of a lack of clinical experience with bosentan in neonates in Japanese and foreign clinical studies, the dosing regimen for this patient population should not be mentioned in the "Dosage and Administration" section of the package insert and that precautions against the use in low-birth-weight infants and neonates should be presented in the "Pediatric Use" section. PMDA concluded that the applicant's proposal was appropriate, and the conclusion was supported by the expert advisors. On the basis of the above discussion, PMDA has concluded that the dosage and administration proposed by the applicant should be provided in the "Dosage and Administration" section (as described below).

[Dosage and administration]

The usual dosage of bosentan for infants and children is 2 mg/kg twice daily (morning and evening) administered orally after being dispersed in a small amount of water. The maximum dose is 120 mg/dose (240 mg/day).

(5) Risk Management Plan (draft)

Based on the discussion in "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1) and comments raised by the expert advisors, PMDA has concluded that the safety and efficacy specifications

listed in Table 31 should be included in the risk management plan for the product and that the additional pharmacovigilance activities and risk minimization activities listed in Table 32 should be implemented. The applicant submitted a draft risk management plan and a draft post-marketing surveillance plan (outlined in Table 33) integrating the specifications, activities, and others shown in Tables 31 and 32.

Table 31. Safety and efficacy specifications in the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hepatic function disorder • Teratogenicity • Pancytopenia, decreased white blood cells, decreased neutrophils, decreased platelets, anemia, decreased hemoglobin • Cardiac failure, congestive cardiac failure • Pulmonary edema associated with pulmonary veno-occlusive disease (PVOD) • Drug interactions (CYP2C9, CYP3A4)	• Testicular disorder, infertility male (sperm count decreased)	For all indications: • Low-body-weight patients (<40kg) • Patients with hepatic function disorder • Patients with renal impairment • Long-term safety Prevention of the onset of digital ulcer associated with systemic scleroderma: • Patients with primary biliary cirrhosis
Efficacy specification		
• Long-term efficacy in routine clinical practice		

Table 32. Outline of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan (pediatric dosage and administration)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance) • Post-marketing clinical study [a]	• Activities to ensure providing information obtained from the early post-marketing phase vigilance • Preparation and provision of information materials for patients

[a] After approval of the product, Study AC-052-378 (which is ongoing) will be continued as a post-marketing clinical study until the product becomes available at the medical institutions participating in the post-marketing study.

Table 33. Outline of the draft post-marketing surveillance plan

Objectives	Investigation of the long-term efficacy and safety in routine clinical practice
Survey type	All-case surveillance
Target patients	Pediatric PAH patients
Observation period	1 year after the start of treatment with the product
Planned sample size	120 patients for the safety analysis
Main items	Hepatic function disorder, hematology test resulst

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted for the data submitted in the new drug application in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products,

Gene Therapy Products, and Cosmetics ("PMD Act"). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the PMD Act for the data submitted in the new drug application (5.3.5.2.2, 5.3.5.2.3, and 5.3.5.2.4). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions. The product is designated as an orphan drug, but the application for the product was submitted for approval of a new dosage for pediatric patients. Tracleer Tablets 62.5 mg containing the same active ingredient as that in the pediatric formulation of bosentan was approved for the indication of pulmonary arterial hypertension in adults in April 2005 and has been used in clinical practice as a standard treatment for nearly a decade. In light of the above facts, PMDA considers that there is no need to conduct a 10-year survey to collect long-term clinical data. Therefore, the re-examination period should be 6 years and 1 day, pursuant to the period requirement (i.e., "a period exceeding 6 years but not exceeding 10 years") stipulated in the provision of Item 1 (a), Paragraph 1, Article 14-4 of the PMD Act. The drug product is classified as a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indication]

Pulmonary arterial hypertension

[Dosage and administration]

The usual dosage of bosentan for infants and children is 2 mg/kg twice daily (morning and evening) administered orally after being dispersed in a small amount of water. The maximum dose is 120 mg/dose (240 mg/day).

[Conditions for approval]

- The applicant is required to develop and appropriately implement a risk management plan.
- Because of the very limited number of patients in the Japanese clinical studies, the applicant is required to conduct a post-marketing drug use-results survey covering all patients treated with the product until data are collected on a specific number of patients, thereby identifying the characteristics of the treated patients. Data on the safety and efficacy of the product should be collected without delay, and necessary measures should be taken to ensure the proper use of the product.